American Heart Journal

An international publication for the study of the circulation

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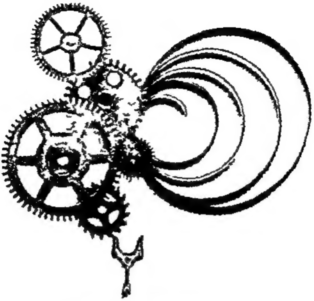

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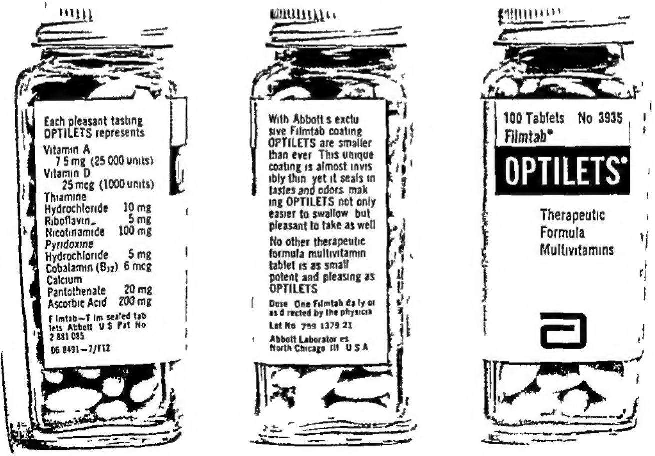

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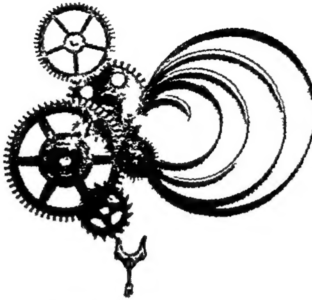

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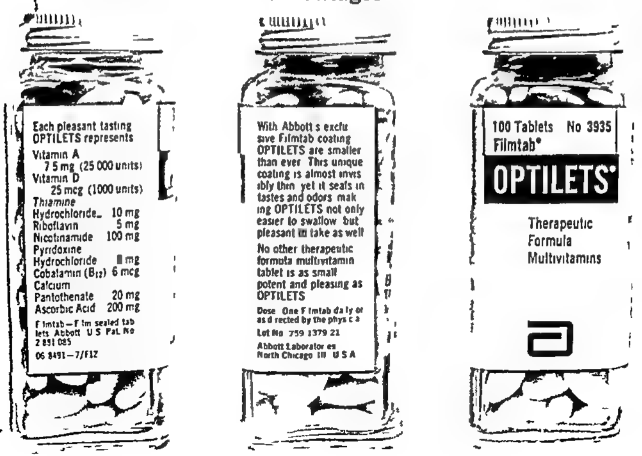

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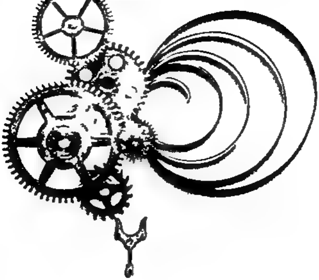

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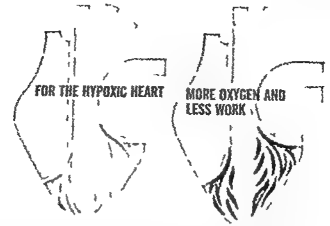

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1 Mann Hubert M D Journal of the Mount Sina Hospital New York May June 1956

2. Huppert, V M D and Boyd L. J M.D F.A.C.P Bulletin New York Medical College Flower and Fifth Avenue Hospitals New York May 1956.

3 Jablons B M D Interamerican Congress of Cardiology Havana, Nov 1956.

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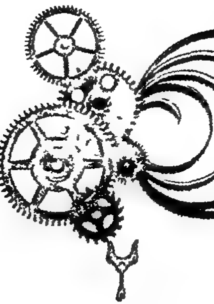

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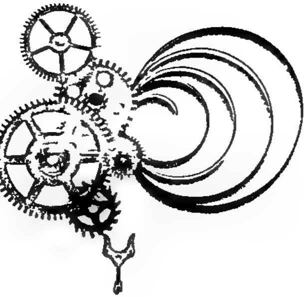

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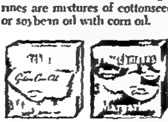

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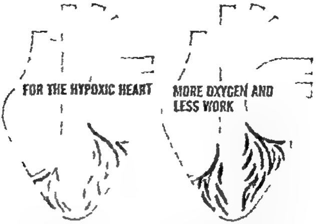

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1. [illegible] Herbert, M.D., Journal of the [illegible] 1956

2. [illegible] M.D., and Boyd [illegible] M.D., F.A.C.P. [illegible] Medical College, Flower and Fifth Avenue Hospitals, New York, May 1956

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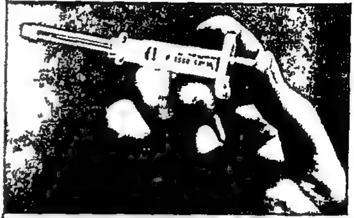

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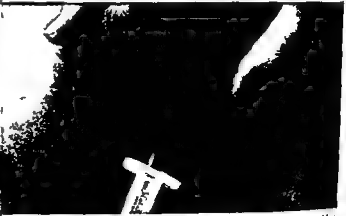

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American Heart Journal

January, 1964 Volume 67 Number 1

Editorial

The heart in kwashiorkor

*A. Swanepoel, M.B., M.R.C.P.**
*P. M. Smythe, M.B., M.R.C.P.***
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Abnormal nutrition has been incriminated in the pathogenesis of various forms of heart disease. Evidence for such a relation ranges from carefully conducted experimental trials[1] to speculation on the role of malnutrition in the etiology of various types of cardiomyopathy. The syndrome of beriberi has been comparatively clearly defined, having passed through phases of clinical description, etiological characterization, and hemodynamic studies. More recently, attention is being directed at metabolic disturbances within the myocardium and the possible delayed implications of such derangements. It is reasonable to postulate that nutritional insults will affect the growing heart of an infant and the adult heart differently, and the question of reversibility of such effects arises. Thus, nutritional deficiency during infancy may conceivably result in the delayed appearance of cardiomyopathy and heart failure in the adult. It is anticipated that answers to these questions are to be found only partially in animal experiments and that a study of appropriate clinical material will ultimately clarify the problem.

The occurrence of a form of protein malnutrition in infancy, now commonly referred to as *kwashiorkor*, provides opportunities in certain parts of the world for such a clinically orientated approach to the problem, but has as yet received scanty attention. In an evaluation of the extent and nature of cardiac involvement in kwashiorkor, several questions arise. The condition should be distinguished from beriberi. Not only are the clinical picture and electrocardiogram different, but it has also been shown that thiamine does not influence the course of kwashiorkor.[2,3] Moreover, elevated levels of pyruvate which have been found in kwashiorkor are not due to a deficiency of thiamine.[4] An additional problem is the diversity of the syndrome of kwashiorkor. Whereas a simple insufficiency of protein is the fundamental cause, several precipitating and complicating phenomena contribute to confuse the picture: infection and toxemia are common, electrolyte imbalance is the rule

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rapid shifts of fluid occur and anemia may add to the heart's burden.

Resulting from protein starvation, muscle wasting is a conspicuous feature. Nevertheless, little attention has been directed to the heart and the probability that it may waste in common with muscle elsewhere has been largely overlooked. Possibly this is because the heart, being a robust organ, has a large structural and functional reserve so that substantial loss of muscle bulk fails to exert clinical effects. However, a cardiac mechanism appears to be the likely cause of the sudden death which not infrequently occurs in severely affected children, often while they apparently are in the process of recovery. This unexpected phenomenon finds a counterpart in the observation that the heart was closer to failure during early rehabilitation than during starvation.[1] Additional evidence of cardiac involvement are clinical features suggestive of reduction in the cardiac output, although no dynamic data are available. The extremities are cold and often deeply cyanosed, pulse amplitude is small or impalpable, capillary bleeding is sluggish, and the skin remains blanched for longer than usual after compression.[2]

Keys and associates[1] were among the first to focus attention on reduced heart size in semistarvation. Since total blood volume remained in the normal range, the reduced cardiac size was attributed to myocardial wasting, and the degree of calculated reduction in volume of the heart (16 per cent) approximated the overall loss of weight (25 per cent). Previously held views that the heart, being a vital organ, enjoyed preferential nutritive status appeared to be incorrect. Similarly, in a large series of children with kwashiorkor the cardiothoracic ratio was significantly decreased. On recovery, serial radiographs tend to show an increase in heart diameter and cardiothoracic ratio. Since a reduction in intravascular volume may contribute to this finding, the observation that the hearts of children who die are frequently greatly underweight provides important confirmation of myocardial wasting. Microscopy does not disclose the nature of this wasting, and has hitherto failed to distinguish between two main alternatives: reduction in the number of myocardial fibers versus shrinkage in the size of individual fibers. Should the former apply, it is likely that an irreversibly depleted muscle will emerge on recovery, which in turn may predispose to heart disease in later life. The observation that all normal hearts, regardless of age, have essentially a similar number of muscle fibers is relevant to this hypothesis. On the other hand, shrinkage of individual fibers would probably be entirely reversible. Distinction between these two possibilities should be resolved by the use of suitable histologic techniques.

Of interest as an expression of cardiac involvement in kwashiorkor are the electrocardiographic changes recorded in most patients.[2] This observation accords with the finding of similar, although less pronounced, changes in the electrocardiogram of starving adult volunteers.[1] The amplitude of all deflections tends to be low, in keeping with reduced muscle bulk; arrhythmias are exceptional, and the most striking alterations are observed in the S-T segment and the T and U waves. Ionic influences undoubtedly play an important part in these latter changes, as may be shown by their rapid reversal within 24 to 48 hours after administration of potassium by mouth. Such ionic patterns are recognized by the occurrence of prolonged Q-T intervals, concave, broad and deep S-T and T depression, and may be distinguished from less rapidly reversible aberrations of the T wave and S-T segment. These changes tend to occur in sequence and permit recognition of an evolving pattern which probably reflects trends in the underlying disease process and which allows some correlation between electrocardiographic appearance and prognosis. In patients who have made a satisfactory recovery, as judged by a gain in weight and normal serum protein values, the persistence of abnormal and often distinctive patterns in the electrocardiogram may constitute a sensitive indication of lingering histochemical abnormalities.

As may be expected, the correlation between these electrocardiographic appearances and morbid anatomic findings has not been established, excepting possibly the low voltages as a manifestation of reduced myocardial bulk. Microscopically, most fatal cases show no myocardial abnor-

malities on the basis of conventional histologic criteria although histochemical techniques may prove to be more rewarding. Appearances suggestive of edema of the myocardium have been noted in some cases coupled with capillary dilatation and congestion vacuolation of myofibrils and variation in the size of individual fibers reminiscent of the changes described in myocardiopathy of unknown origin in the adult African.[7,8] There is also a similarity between electrocardiographic patterns recorded in patients recovering from kwashiorkor and those described in adult Africans with no evidence of heart disease.[9] Such patterns in adult Africans have been regarded as genetically determined variants on the one hand and as a reflection of acquired myocardial abnormality on the other. The fact that almost identical patterns emerge during the course of kwashiorkor and eventually revert to accepted normality regardless of racial group may favor the latter view. These observations may assist in the ultimate identification of malnutrition as the basic cause of the currently obscure form of myocardiopathy which constitutes the most common type of heart disease in the African.

Kwashiorkor is essentially a disease induced by depletion of protein and it is tempting to relate the clinical evidence of cardiac involvement to recent biophysical views on the role of protein in heart failure. The contractile apparatus of myofibrils is provided by specialized protein units which serve to translate chemical to kinetic energy. Evidence is accumulating that these proteins are disturbed under circumstances of heart failure. Thus actomyosin bands prepared from failing hearts do less work under standardized conditions than do bundles from normal hearts[10] changes have been observed in myosin molecules of failing heart muscle[11] decreased protein synthesis has been reported in failing rabbit heart as measured by the rate of uptake of S^{35} labeled methionine.[12] Such disturbed synthesis of protein may be connected with loss of kinetic energy of myocardial contraction. These studies involve the use of myocardium from hearts caused to fail under mechanical or anoxic stress and extrapolation to the protein depleted heart in kwashiorkor (and analogous deficiency states) is not yet justified. However similar techniques applied to malnourished hearts may help to clarify the relation between protein metabolism and heart failure.

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The electrocardiogram of the premature infant

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Numerous studies on the electrocardiograms (ECGs) of premature babies have been published since the original report of Nicolai and Funaro[1] in 1908. Hecht and Noeggerath[2] included premature infants in their bipolar lead studies in 1913. Burghard and Wunnerlich,[4] working with 32 babies who weighed less than 2,500 grams each and in whom tracings were taken at various ages between 9 hours and 2 months, concluded that a typical *electrocardiographic pattern for premature* infants does not exist. Master, Dack, and Jaffe[5] in 1935 and Castelfranco and Guzzetti[6] in 1952 attempted a more detailed investigation of precordial leads. Stoermer[7,8] found somewhat shorter intervals for the various ECG time components as well as high and pointed P waves and frequently small deviations of the S-T segment. Gomirato-Sandrucci and Crosato,[9] studying 100 babies from 1 to 10 days of age whose birth weights ranged from 320 to 2,500 grams, also commented on the same findings in regard to the P wave and S-T segment. In addition, they pointed out that premature infants had ECGs which were suggestive of a more pronounced right ventricular hypertrophy than those of normal term babies.

Vamont[10] analyzed the cases of 70 babies whose weights ranged from 900 to 2,500 grams and found no substantial differences in the ECGs between weight groups. Lepeschkin,[11] summarizing various studies, stated that premature infants might have a lower ECG voltage and the QRS a less marked right axis deviation than those of normal infants. Not rarely, P waves were higher and of greater duration, especially in groups of infants of lesser weight. Q-T duration was found to be prolonged parallel to the deficiency in weight.

Recently, studies appeared by Hubsher,[1] with 143 cases divided into [illegible] age-weight groups, and by Wenger, Watkins, and Hurst,[13] with serial tracings of 7 cases.

Our study was undertaken in order to determine, with a larger number of serial tracings, the characteristic features of the ECG of the premature infant, with particular reference to the weight and age of the baby.

Material and methods

Three hundred and sixty-four electrocardiograms of 88 infants who were born prematurely at the Charity Hospital of Louisiana were taken by the same person using the same apparatus (a direct-writing Sanborn Visette).

Of 88 babies, there were 37 males, 50 females, and 1 of undetermined sex. Among the males, 33 were Negro and 4 were

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white of the female infants 45 were Negro and 5 were white All babies remained quiet in the supine position in the incubator or crib while the ECGs were being recorded some of the infants were pacified with nipples but none was sedated Infant size electrodes were used with alcohol sponges to reduce skin resistance the pre cordial electrode was retained by a chest strap fashioned according to the recom mendations of Glendy and Glendy [14]

The tracings were obtained at prede termined intervals from shortly after birth to 30 hours 36 to 90 hours and at weekly intervals to 7 weeks Recordings were dis continued whenever babies were discharged from the nursery and every electrocardio gram had at least 12 leads (standard aug mented unipolar and Precordial Leads V_1 to V_6 The weight of the patient was de termined at the time of every tracing

The electrocardiograms were analyzed with reference to the time components (duration of P P R QRS Q T and R R) the height in millivolts of the QRS and T deflections in Leads V_1 and V_6 The voltage of the P wave and of the S T segment when shifted was measured at the lead where it was most pronounced

Vectors were plotted from the maximal P QRS and T deflection amplitudes as well as from the initial and final parts of the QRS Thus ventricular depolarization is represented by three component vectors as proposed by Peñaloza and Franchesi [15] The initial or early vector of the QRS refers to the orientation of electrical forces at the onset of depolarization and not at a specified time such as the 0 02 second vector Since the initial portion of the QRS could be isoelectric in a particular lead (the initial vector being perpendicular to that lead) the 0 02 second vector could only be determined if reference leads had been taken simultaneously Likewise the ter minal vector is related to the final potentials of ventricular depolarization without ref erence to time Although these measure ments are not truly vectorial since mag nitudes are not evaluated they are useful in

Table I Distribution of patients by weight and age

Weight group	*Age group*							*Total number of tracings*
	0–30 hr	*36–90 hr*	*1 wk*	*2 wk*	*3–4 wk*	*5–7 wk*	*8–12 wk*	
Group IV (2 000 2 700 grams)	12 (14 0%)	5 (6 7%)	7 (9 9%)	8 (13 3%)	8 (17 8%)	5 (21 7%)	1 (25 0%)	46 (12 6%)
Group III (1 600 1 990 grams)	37 (43 0%) 1d	38 (50 7%)	29 (40 8%)	23 (38 4%)	18 (40 0%)	13 (56 5%)	2 (50 0%)	160 (44 0%)
Group II (1 200 1 590 grams)	25 (29 0%) 2d	22 (29 3%)	25 (35 2%)	21 (35 0%)	16 (35 5%)	4 (17 4%)	1 (25 0%)	114 (31 3%)
Group I (400 1 190 grams)	12 (14 0%) 5d	10 (13 3%) 1d	10 (14 1%) 1d	8 (13 3%)	3 (6 7%)	1 (4 4%)	0	44 (12 1%)
Total number of patients	86 8d	75 1d	71 1d	60	45	23	4	364

A tu l ad n with per nt cl ne l pa entheses. F gures f llowed b the lett d p sent th n be f surv o each g weight group

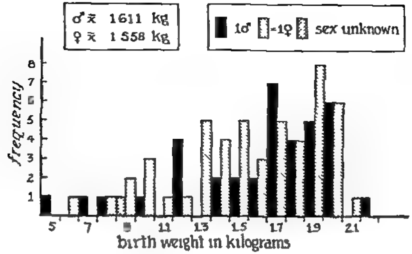

Fig. 1. Distribution of weights by sex in the first age-group. *Sex unknown* refers to a patient that presented at birth both male and female genitalia. Weight did not appear to be related to sex, and the difference between means is not significant. t = 0.6330; p 0.5.

Table II. Minimal, mean, and maximal measurements of the spatial QRS-T angle and the frontal and horizontal projections of the P, initial, maximal, and final QRS and T vectors

	QRS-T (Spatial) (degrees)	P (degrees)		Initial QRS (degrees)		Main QRS (degrees)		Final QRS (degrees)		T (degrees)	
		F	H	F	H	F	H	F	H	F	H
0-30 hr (Min.)	0	15	0	−165	0	30	−22	[illegible]	−180	−135	−180
0-30 hr (x̄)	87	60	51	0	[illegible]	114	[illegible]	171	−118	42	−68
0-30 hr (Max.)	180	[illegible]	[illegible]	165	135	−135	−68	−105	−68	150	180
36-90 hr (Min.)	15	15	0	−165	0	45	−45	75	−180	−90	−158
36-90 hr (x̄)	101	56	51	−5	[illegible]	108	116	165	−118	18	−56
36-90 hr (Max.)	180	[illegible]	68	135	135	−75	−90	−45	−68	90	90
1 wk (Min.)	15	15	22	−165	22	15	−68	75	−180	−75	−90
1 wk (x̄)	82	56	53	−30	[illegible]	104	108	172	−116	[illegible]	−56
1 wk (Max.)	180	90	68	135	158	−75	−90	−30	−68	90	68
2 wk (Min.)	15	15	0	−105	22	15	22	75	−180	−30	−90
2 wk (x̄)	74	54	52	−13	77	104	114	166	−113	44	−51
2 wk (Max.)	165	90	68	135	158	−75	−90	−45	−68	120	68
3-4 wk (Min.)	15	15	22	−165	22	−30	−22	105	−180	−15	[illegible]
3-4 wk (x̄)	63	52	52	−19	69	98	112	171	−116	54	−76
3-4 wk (Max.)	150	[illegible]	68	75	158	−75	180	−135	−68	105	0
[illegible] wk (Min.)	[illegible]	15	0	−135	22	15	−22	105	−158	15	−68
[illegible] wk (x̄)	56	50	53	−41	[illegible]	100	94	169	−114	43	−45
[illegible] wk (Max.)	120	[illegible]	68	60	135	120	158	−135	−90	75	22

F, Frontal; H, Horizontal. [illegible] 0 degree is at [illegible] (see Figs. 3 and 4) [illegible] half [illegible] positive [illegible] For the frontal plane conventional [illegible] were used.

indicating the general shape and direction of the vectorcardiographic loop that would be obtained using the same leads

The spatial QRS T angle was estimated from the maximal QRS and T vectors by use of a three-dimensional model representing the extremity and precordial leads. This model was constructed according to the description given by Penaloza and Tranchesi[15]

The data were analyzed with the help of an IBM 650 digital computer*

According to the World Health Organization[16] a birth weight equal to or less than 2 500 grams was the criterion for prematurity. So that a random sample of premature babies could be obtained no attempt was made to select patients in any way other than by birth weight

Ten infants died 1 for whom there were three ECGs 1 with two tracings and the others with only one tracing each (Table I) These ECGs were analyzed separately but proved to be no different from those of the survivors. All statistics were calculated with the nonsurvivors as part of the total group

Results

Birth weights varied from 500 to 2 200 grams (Fig 1) Weight did not present a statistically significant difference between sexes at birth or thereafter. Throughout this study a p value of 0 05 or less was accepted as the level of statistical significance

All babies were divided into 7 age groups which corresponded to the times at which ECG tracings were taken 0 to 30 hours 36 to 90 hours 1 week 2 weeks 3 to 4 weeks 5 to 7 weeks and 8 to 12 weeks These age groups were then subdivided into 4 weight groups yielding 28 age weight groups as shown in Table I This was done in order to ascertain the separate influence of age and weight on the electrocardiograms If one considers that smaller infants are probably more premature this permitted also an evaluation of the probable ECG modifications related to the degree of prematurity

The average heart rate increased with age from 125 per minute for the first age group to 170 per minute for the 5 to 7 week age group and a normal sinus rhythm was present in all tracings The durations of P R and QRS (Fig 2) were very similar throughout the different ages with a mean difference of 0 039 second The P R interval decreased by an average of 0 02 second during the first 90 hours and changed little after that age The Q T (= Q T $\sqrt{R\,R}$) decreased markedly with age although at a slower rate than the corresponding cycle length

The mean maximum height for the P wave was observed in the second age group and the tallest P (0 4 mv) in the fifth age group The average height decreased gradually to approach in 5 to 7 weeks the same amplitude is that seen in the first age group (0 14 mv) In the majority of cases the greatest voltage of P was seen in Standard Lead II and rarely

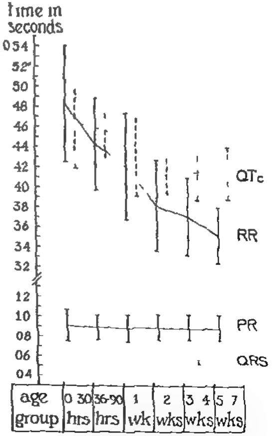

Fig 2 Duration of the Q T (Q T / $\sqrt{R\,R}$) P R and QRS intervals at different ... Brackets encompass ± one stand... the mean

*Through the courtesy of the Computer Center Tulane University New Orleans La.

in precordial leads The P axis was remarkably constant mean values changed only 10 degrees in the frontal plane up to 7 weeks of age (Table II)

In two tracings (1 week and 2 weeks) isoelectric P waves were present in Lead I A diphasic P sometimes occurred in Leads V_1 and V_2 but was always positive from Lead V_3 to Lead V_6

The initial ventricular depolarization vectors presented in the frontal plane projection a wide scatter which diminished with age (Figs 3 and 4) All vectors were in an anterior or left lateral direction in the first age group shifting to a more anterior position with increasing age Seven vectors in the 0 to 30 hour age group and 9 in the 1 week age group were rightwardly directed producing q waves in Lead I

The final QRS vector occupied a position opposite to the initial vector in the horizontal plane Except for one instance at 1 week of age all were directed posteriorly and mainly to the right There were only 3 instances of a leftwardly directed final vector (no S wave in Lead I)

The vector plotted from the maximal QRS deflections was usually directed to the right downward and anteriorly but in 4 babies in the first age-group a markedly posterior orientation was observed (Figs 3 and 4) This is unusual because a right ventricular preponderance is to be expected At 1 week of age 2 babies had the maximal QRS at -80 and -140 degrees both directed posteriorly

The T vectors were usually well separated from the QRS In the first age group both anterior and posterior orientations were found with a predominance of the latter From the second age group onward a *tendency toward a leftward and* posterior orientation was observed These modifications are translated by the increasing positivity of T in Lead V_6 and the modifications of right precordial leads with age (Figs 6 and 7)

The average spatial QRS T angle increased to 100 degrees in the second age group and then gradually decreased to nearly half that value in the 5 7 week age group (Table II) A q wave in Lead V_1 was present only twice in the first two age groups and once each in the next two age groups Only once was the q wave greater than 0 05 mv in Lead V_1 The average voltage of R and S increased until 2 weeks of age and then decreased in the ensuing age groups (Fig 5) the average *R/S* ratio remained positive A positive T wave was found in Lead V_1 in 22 per cent of the infants between birth and 30 hours of age This incidence decreased to 4 per cent in the next age group and from then on all T waves were negative except for one instance at age 2 weeks and another at 5 7 weeks The T became more negative on the average until the second week and thereafter became less negative

Our data disclosed no visible trend for the different weight groups except for 2 instances in the 0 30 hour age group The incidence of positive T waves in Lead V_1 and a q in Lead V_6 was relatively greater in the heavier weight groups (Table III) These differences are statistically significant No such differences were observed for T waves in Lead V_6 q in Lead V_1 (only 2 cases) or any other measured variable

In Lead V_6 a q wave was present in 21 per cent of the ECGs in the first age group (Table III) This incidence doubled in the next age group tripled in the 1 week age group and persisted through the seventh week The R in Lead V_6 appeared to increase throughout the six age groups as the babies grew older whereas the S declined a mean of only 0 1 mv throughout the 7 weeks (Fig 5) This is to be expected from the leftward shift of the QRS axis with age A negative T in Lead V_6 was present in 26 per cent of the babies in the first age group and in only 4 and 6 per cent of the babies in the second and third age groups respectively

Deviations of the S-T segment from the *isoelectric line were observed with in*creasing frequency until the second week (Table IV) We have indicated only the lead in which the maximal S T shift was observed This occurred most commonly in right precordial leads especially Lead V_1 The largest values were -0 2 mv (in Lead V_1) and $+0$ 2 mv (in Lead V_4)

Of the 10 nonsurviving babies autopsy revealed an atrial septal defect and slight ventricular dilatation in one in whom death was attributed to pulmonary congestion and atelectasis *In the other 8* babies examined post mortem no structural

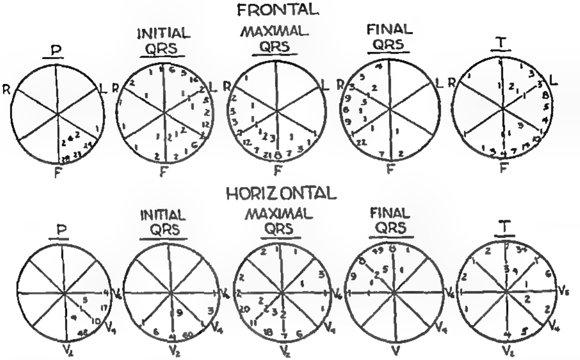

Fig 3 Distribution of the P, initial, maximal, and final QRS, and T vectors for all cases in the 0 to-30 hour age-group. Numbers indicate actual incidence. Surviving cases are represented in the periphery of each circle whereas the figures at more centrally located areas refer to nonsurvivors. Letters *R*, *L*, and *F* (frontal plane) indicate the positions of the unipolar leads aV_R, aV_L, and aV_F, whereas V_2, V_4, and V_6 (horizontal plane) represent the precordial lead

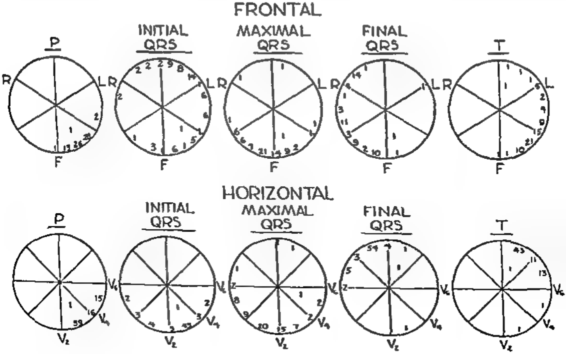

Fig 4 Same as Fig 3 at 1 week of age

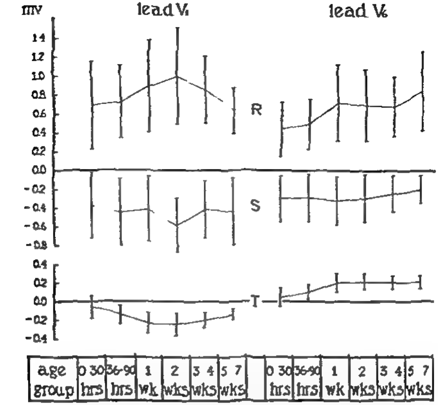

Fig. 2. Amplitude of R, S, and T in precordial Leads V_1 and V_6 in the different age-groups. Brackets encompass ± one standard deviation from the mean.

cardiac abnormality was observed. In one case autopsy was not done but no clinical evidence of cardiac disease had been observed. The ECGs of the nonsurvivors could not be differentiated from those of the others, as may be seen in Figs. 3 and 4, in which the vectorial orientations of these infants are compared.

A number of correlations were attempted between ECG measurements and the sex of the infants, but significant results were not obtained.

Discussion

Comparing our results with data for full-term infants obtained by Ziegler[17] we noticed that *on the first day of age* the average QRS axis of the premature infants had a less marked rightward displacement, whereas the average T axis was in a more horizontal position. Therefore the QRS-T angle was much the same in the premature and full-term newborn infants. In the ensuing days the T vector shifted leftward, whereas the QRS was displaced to a smaller degree in the same direction, both in full-term and premature infants, increasing the average QRS-T angle to the maximum value observed in infants. At the first week and thereafter this angle decreased progressively with age.

The Q-T index was found to be prolonged, especially in the early age groups. This cannot be attributed to hypothermia, since during the first days the babies were kept in incubators under controlled temperature. Probably the Q-T corrected according to Bazett's formula ($QT = QT / \sqrt{RR}$) fails to compensate for tachycardia and also for sudden changes in heart rate,[18] as may be expected from the manipulation required for the attachment of the electrodes.

Deviations of the S-T segment in the ECG of the premature infant has been observed frequently[7,9,11] and has been related to such factors as hypoxia and electrolyte imbalance. In our series the S-T, when shifted, was usually in a negative direction in right precordial leads and

Table III Incidence of q waves in Lead V_6 and negative isoelectric (or isodiphasic) and positive T waves in Leads V_1 and V_6 for the different weight groups of the 0 to 30 hour age group

	q in Lead V			*T in Lead V_1*			*T in Lead V_6*		*Tota*
	Absent	*Present*	*Total*	*— or iso*	+	*Total*	*— or iso*	+	
Group IV (2 000 2 700 grams)	9	3	12	8	4	12	5	7	12
Group III (1 600 1 990 grams)	23	14	37	25	12	37	28	9	37
Group II (1 200 1 590 grams)	24	1	25	23	2	25	14	11	25
Group I (400 1 190)	12	0	12	11	1	12	6	[illegible]	12
Total	68	18	86	67	19	86	53	33	86
χ^2_3	14 023			9 758			6 148		

I d cates p < 0 05
Th ch sq test w ot ppl d f t e q n Lead V becaus t occurred n ly 2 cases.

*Table IV Per cent incidence for each age group of the maximal S T segment deviation observed**

Age	*Incidence for different leads†*									% Total‡
	I	*II*	*III*	V	V_1	V	V	V	V	
0 30 hr		1 2			16 3	5 8	1 2			24 5 (71)
36 90 hr		1 3			30 7	9 3			1 3	42 6 (32)
1 wk		2 8	1 4		38 0	11 3	1 4			54 9 (39)
2 wk		3 3			43 3	8 3	3 3		1 7	59 9 (35)
3 5 wk		4 4	2 2		76 7	2 2			2 2	37 7 (17)
5 + wk			4 3	4 3	17 4	13 0		4 3		43 3 (10)

*Only t es f at least 0 1 mv we rec ded Th gre te t devi t wa observed n Lead I r V
†Lead i wh h maximal S-T h ft were bserv d
‡Actual cid ce pare these

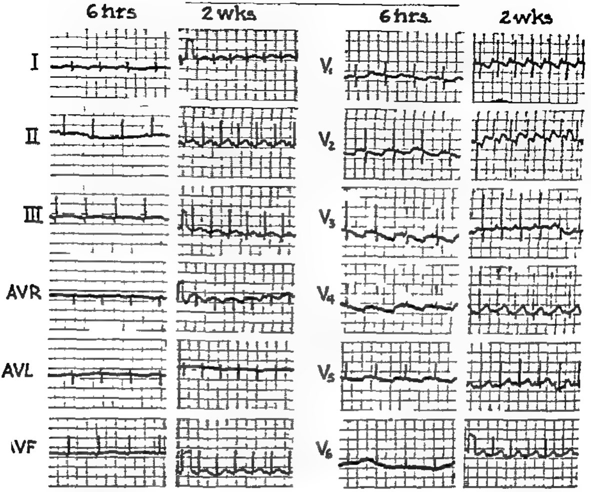

Fig 6 Patient No 6 Electrocardiogram of a female infant of the lighter weight-group In the tracing at 6 hours of age (patient weight = 990 grams) the T vector is oriented posteriorly and at 2 weeks (patient weight = 930 grams) it has a more lateral orientation as seen by the shift in precordial transition zone The T vector is also of greater magnitude The QRS axis has not changed appreciably Note also the higher voltage of P in the second tracing with peaking in Lead V_1 All leads have a normal standard

occasionally also in Standard Leads II and III the same as has been found in association with physiologic right ventricular hypertrophy

The average P amplitude was much the same for premature and full term babies. *Occasionally we recorded high (0 4 mv)* and pointed P waves of the pulmonale type in Lead II or Lead V_1 In contrast the R S and T voltages in precordial leads were on the average lower in premature infants whereas the R/S ratio was generally larger in both right and left precordial leads

A q wave in Lead V_1 is rarely observed *both in premature* and full term infants but a q in Lead V_6 is present in approximately three fourths of the ECGs of normal full term infants on the first day of life according to Ziegler[17] In our series less than one fourth of the tracings from infants at this age presented a q in Lead V_6 and this incidence was significantly more common in the heavier weight groups

According to Datey and Bharucha[19] the T in Lead V_1 is generally positive in normal infants at birth and during the first day of life and it becomes inverted by the age of 4 to 7 days In our group the T was upright in this lead in less than one fourth of the tracings from infants up to 30 hours of age and as was observed by Hulsher[1] this incidence was also significantly larger for the premature infants of heavier weight

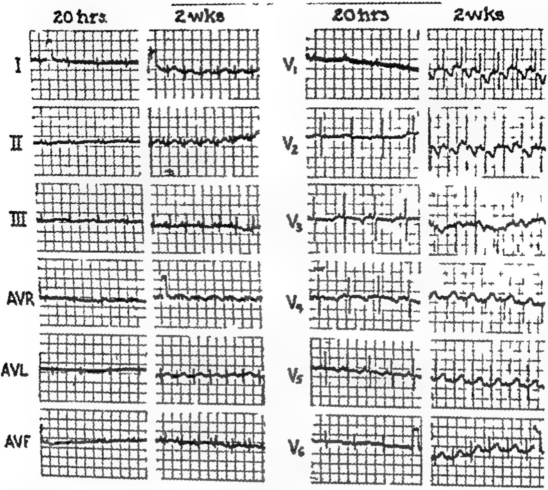

Fig 7 Patient No 58 Electrocardiograms of a male baby in the heavier weight group Changes in the T waves are marked between 20 hours of age (patient weight = 2 250 grams) and 2 weeks (patient weight = 2 070 grams) The T vector shifted from a posterior to a more lateral position and increased in magnitude Note peaked P wave in Lead II III and aVF The voltage of QRS in the limb leads is smaller than for the infant of lighter weight in Fig 6 Normal standard on all leads

In other words these differences with respect to the full term infant were more accentuated in the presumably more immature infants

Summary

1 Serial electrocardiograms were taken on 88 premature infants from birth to 7 weeks of age The tracings of the same age group were subdivided into 4 weight groups

2 Ten infants died 8 of these contributed tracings only for the first age group Those electrocardiograms proved to be no different from the tracings obtained in the surviving infants and were included in the total group for statistical purposes

3 Mean heart rate increased with age from 125 at birth to 170 bpm at the oldest age group studied whereas the Q T was found to be relatively prolonged Tall and pointed P waves were found occasionally in Leads II and V_1 whereas the QRS voltage was frequently lower than that of normal full term babies

4 The average P axis remained between 50 and 60 degrees for all age groups The maximal QRS and T axes presented a wide scatter in both the frontal and horizontal planes The QRS axis was usually directed rightward downward and anteriorly except for 4 babies in the first age group in whom a marked posterior orientation was observed The T axis was directed

leftward and posteriorly forming an angle with the QRS axis which increased until the infants were 90 hours old and which then gradually decreased with increasing age The initial vectors of the QRS were oriented in an anterior or left lateral direction becoming more anterior with age whereas the final vectors tended to be situated in an opposite direction

5 The only findings that could be related to the weight of the infants were the significantly greater occurrence of a q in Lead V_6 and of negative T waves in right precordial leads in babies who were lighter in weight These changes probably reflect *a greater degree of immaturity*

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The serum transaminase (S-GOT) and electrocardiogram in autopsy-confirmed acute myocardial infarction

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Our initial experience with serum glutamic oxaloacetic transaminase (S-GOT) as a measure of myocardial necrosis including the data from 18 autopsied patients was reported in 1956.[1] Complete agreement was seen between increased activity of S-GOT and the histopathologic diagnosis. The present paper extends the earlier observations by reviewing an additional group of patients with acute myocardial infarction coming to postmortem examination.

Method

One hundred and fifty-seven consecutive autopsies of patients with an acute myocardial infarction were reviewed covering a period of 44 months from August 1957 to May 1961. The clinical course and complications of the terminal illness were evaluated along with the electrocardiographic and laboratory observations. This information was obtained from the clinical records of the patients and the autopsy protocol. Of the 157 patients, 39 had had one or more determinations of S-GOT during hospitalization. The tests were done by the method of Reitman and Frankel. The normal limits for serum transaminase activity by this method are 8 to 40 units per milliliter; values from 41 to 50 are borderline and those above 50 units per milliliter are abnormal.

Results and comment

Fig. 1 is the scattergram of the S-GOT results plotted for each day from the clinical onset of myocardial infarction. The mean of all the tests and the maximum value for each day are indicated in Fig. 2. The mean peak for all patients in the group was 236 units per milliliter. One patient with increased S-GOT is not included because it was impossible to date the onset of the acute attack. Another patient with shock and congestive heart failure had transaminase activity which ranged from 2,375 to 4,150 units per milliliter. Liver function studies were abnormal and centrilobular liver necrosis was found at autopsy. The data from this patient were excluded from the calculation of the mean and maximum transaminase values because of the distortion introduced.

The correlation of the S-GOT results with the autopsy findings is presented in Table I. Of the 39 autopsied patients, 36 or 92.3 per cent had one or more values

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leftward and posteriorly, forming an angle with the QRS axis which increased until the infants were 90 hours old, and which then gradually decreased with increasing age. The initial vectors of the QRS were oriented in an anterior or left lateral direction, becoming more anterior with age, whereas the final vectors tended to be situated in an opposite direction.

5. The only findings that could be related to the weight of the infants were the significantly greater occurrence of a q in Lead V_6 and of negative T waves in right precordial leads in babies who were lighter in weight. These changes probably reflect a greater degree of immaturity.

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other 7 patients there were no changes in the electrocardiogram to permit identification of an acute process Five of the 7 patients had two or more serial tracings

In the 7 patients without diagnostic changes the electrocardiographic findings included the following Q waves of abnormal duration and inverted T waves consistent with an old myocardial infarct in 3 changing supraventricular arrhythmias in 2 poor progression of precordial R wave voltage and subendocardial ischemia in 1 and myocardial ischemia in 1 Hence these results confirm previous observations that the electrocardiogram is not diagnostic of an acute myocardial infarction in a significant number of instances particularly when the tracing displays residuals of a previous infarct

The observations of this study confirm the previously reported correlation between high serum transaminase activity and mortality [3,4] In a comparison of the data from the 60 patients with transmural myocardial infarction and a 26 per cent mortality in our earlier study [1] it is noted that the average and maximum values of S GOT by the day are consistently higher

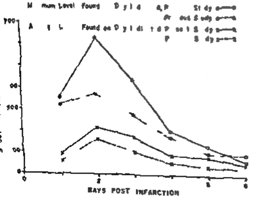

Fig 2 Average and maximum levels of S-GOT plotted by the day from clinical onset

in the fatal cases of the present study (see Fig 2)

Summary and conclusions

The cases of 157 consecutive patients with autopsy-confirmed acute myocardial infarction were reviewed Thirty nine patients were found to have had one or more determinations of the serum transaminase (S GOT) Increased S GOT activity was noted in 92 3 per cent of the patients or in 97 3 per cent if the 2 patients were excluded who died within 24 hours and in whom only one enzyme determination was available

The electrocardiogram was diagnostic of the acute process in 31 of the 38 patients (81 5 per cent) in whom tracings were available

The average and maximum daily S GOT values support in general the relationship between high transaminase activity and mortality

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Antiheparin and antifibrinolytic activity of blood in patients with atherosclerosis

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In recent years there have been many discoveries clarifying the causes of the tendency to thrombosis in atherosclerotic blood vessels. Professor Kudryashov of Moscow University showed that one of the major factors in the tendency to thrombosis is a disturbance in the physiologic anticoagulant system. Our work and that of our collaborators has shown that these disturbances appear initially in patients with atherosclerosis. The activities of heparin and active fibrinolysin are decreased in patients with atherosclerosis. In attempting to determine the mechanism of this decrease in activity, we have investigated the activity of inhibitors of heparin and fibrinolysin—antiheparin and antifibrinolysin.

Materials and methods

Because of the observation that the anticoagulant action of heparin added to normal plasma is diminished by the addition of aged serum, Poller[13] studied the possible connection of this antiheparin activity and the appearance of thrombosis. This antiheparin activity does not depend on the activity of Factor VII or the Christmas factor and is not diminished by therapy with phenindione. A correlation was thought to exist between the antiheparin activity of serum and the appearance of thrombosis.

Antiheparin activity was assayed by the following method. To 5 ml. of venous blood was added 0.21 ml. of a mixture of 1.6 per cent potassium oxalate and 2.4 per cent ammonium oxalate. From this, 0.2 ml. of plasma was placed in a water bath at 37°C. and mixed with 0.1 ml. of heparin solution (2 units per milliliter) and 0.2 ml. of the serum to be tested. To this mixture was added 0.2 ml. of 0.18 per cent calcium solution, and the coagulation time was measured.

It has been known that under certain conditions the blood of animals and man demonstrates inhibitory activity against fibrinolysin (plasmin). In recent years the studies of Sandberg, Tsitouris and collaborators[14,16] have demonstrated an increase in the antifibrinolytic activity of the blood of patients with acute thromboses and myocardial infarction.

The antifibrinolytic activity of blood can be determined by several methods. The method developed by Sandberg and associates[15] is based on the measurement of the time required for lysis of a fibrin clot by a standard solution of fibrinolysin with and without the addition of the plasma to be tested. The method of Biezenski[15] is based on the determination of the inhibitory activity of increasing dilutions of the serum to be tested on a standard solution of fibrinolysin. The normal fibri

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nolytic activity of serum by this method is 11/20 to 1/210 dilution

We used the method of Sandberg and collaborators A mixture of fibrinogen solution (1 per cent) 0 2 ml human thrombin (20 units per milliliter) 0 2 ml plasma 0 2 ml and thrombolysin 0 4 ml was incubated in a water bath at 37 C and the time required for lysis of the clot was measured The thrombolysin was made up in dilutions of 1 10 1 20 and 1 40 from a stock solution with activity of 2 000 units per milliliter so that the final activity of thrombolysin in the mixture was 80 40 and 20 units per milliliter This preparation loses its activity quickly therefore utilization should be prompt

The subjects tested were a control group of 20 healthy male donors from 35 to 55 years old a group of 30 men from 36 to 60 years old with early manifestations of atherosclerosis and a group of 30 persons with advanced atherosclerosis The persons in the latter group all had frequent attacks of angina pectoris and a past history of myocardial infarction

Results

Antiheparin activity We observed a distinct increase in the antiheparin activity of blood in the patients with atherosclerosis Table I shows the data from the control group

In patients in the early stage of coronary atherosclerosis manifested by angina pectoris of recent onset and no evidence of myocardial infarction there was a tendency toward an increase in the activity of antiheparin In the majority of patients in this group the activity varied within the range of 1 50 to 3 20

In patients in the advanced stages of atherosclerosis with a past history of myocardial infarction and evidence on the electrocardiogram and ballistocardiogram of coronary insufficiency a more pronounced increase in the antiheparin activity of blood was observed All of them had levels of activity less than 2 10 (Table II) Thus the development of the atherosclerotic process is accompanied by an increase in the antiheparin activity of blood

Antifibrinolytic activity In the control group of healthy donors the results were comparable to those of Sandberg and associates The antifibrinolytic activity in 80 units of thrombolysin was 200 ± 60 seconds in 40 units it was 460 ± 110 seconds and in 20 units it was 730 ± 150 seconds

In the group with early atherosclerosis there were no changes in the antifibrinolytic activity of blood in contrast to the decrease in antiheparin activity which occurred in the same group (see Table III)

With 80 units of thrombolysin the level of activity varied from 150 to 300 seconds and with 40 units of thrombolysin it varied from 470 to 610 seconds However in the group with advanced atherosclerosis changes in the level of antifibrinolytic activity were found In most cases the activity was more than 260 seconds in 80 units of thrombolysin and more than 470 seconds in 40 units of thrombolysin The activity remained at a normal level in only 7 patients of this group Thus the development of the atherosclerotic process is also accompanied by an increase in the antifibrinolytic activity of blood which concomitant with a decrease in fibrinolytic activity could be a factor in the predisposition to thrombosis

Recently heparin and fibrinolysin have been used with great success in the therapy of acute thromboses It was of interest to study the level of activity of antiheparin and antifibrinolysin in the blood of patients under such therapy Fibrinolysin (obtained from Prof B A Kudriashov Moscow University) was used in 37 cases of vascular thromboses (Table IV)

The agent was used in combination with small doses of heparin (20 000 to 30 000 units per day) administered by intravenous drip over a period of 3 to 4 hours with repeated injections when necessary on the second and third days (Table IV)

Therapy with heparin and fibrinolysin was not effective in one case of thromboembolism of the pulmonary artery and in cases of myocardial infarction over 1 day old In our opinion this therapy is promising in the first few hours after myocardial infarction The necessity of combined therapy with heparin and fibrinolysin should be stressed since this combination mimics the physiologic anticoagulant reaction to thrombosis in the organ

Table I. Antiheparin activity of blood of healthy persons

Number of cases	Antiheparin activity
1	2 20
2	2 30
3	2 40
1	2 50
3	3 00
1	3 10
3	3 20
1	3 30
2	3 40
1	3 50
2	4 00

Table II. Antiheparin activity of blood of patients with atherosclerosis

Antiheparin activity	Initial stage	Later stage
3 20	4	–
3 10	4	
3 00	5	
2 50	2	
2 40	4	
2 30	2	
2 20	3	
2 10	2	1
2 00	2	1
1 50	2	2
1 40	–	3
1 30	–	5
1 20	–	4
1 10	–	3
1 00	–	7
50	–	2
40	–	1
30	–	1

Average 2 44

Possibly the lack of therapeutic effect reported by Richter[14] and others resulted from the use of fibrinolysin alone. In our patients who were receiving fibrinolysin and heparin, even those with severe myocardial infarction with cardiovascular collapse experienced a less complicated postinfarction period than did patients who were not receiving these agents. In some cases we observed a disappearance of the electrocardiographic signs of coronary insufficiency. Usually cardiac pain disappeared during treatment. The efficacy of therapy is best demonstrated by the data on the levels of transaminase in the serum. Fig. 1 demonstrates that the increase in the levels of transaminase was significantly less in the patients treated with fibrinolysin.

We found that during therapy there was a significant decrease in the level of activity of antiheparin in the blood. When the blood was tested one half hour after the administration of heparin and fibrinolysin, the levels of activity were greater than 30. The low levels of antiheparin remained on the second day of therapy. The changes in the level of antifibrinolytic activity are more complicated. Tsitouris and associates noted that the level of activity usually decreased after therapy with fibrinolysin. He observed low levels of activity varying from 120 to 200 seconds in the first hour after therapy in 14 of 16 cases. However

Table III. Antifibrinolytic activity of blood of patients with atherosclerosis by 80 units of thrombolysin

Initial stage	Antifibrinolytic activity (sec.)	Later stage
6	150–180	
6	180–210	
9	210–240	
4	240–270	5
5	270–300	2
	300–330	7
	330–360	8
	360–390	4
	420–450	1
	450–480	3

Table IV

Type of involvement	Number of cases
Thromboembolism of the arteries to the lower leg and foot	10
Thrombophlebitis of the veins of the pelvis and calf	4
Thromboembolism of the pulmonary artery	3
Thromboembolism of cerebral vessel	1
Myocardial infarction on the first day	15
Myocardial infarction on the second day	4

on the second day after 18 to 20 hours the levels increased to the range of 270 to 600 seconds the range occurring in patients with advanced atherosclerosis

To clarify the nature of the influence of fibrinolysin on inhibitory factors in the blood we conducted investigations in 10 rabbits in which lipoid deposits in the vessels had been produced by the feeding of cholesterol for 3 months The levels of antifibrinolysin were determined before the administration of fibrinolysin and on the second day after administration of fibrinolysin The levels of activity of antifibrinolysin varied from 130 to 180 seconds (with 1 unit of fibrinolysin) before the administration of fibrinolysin and increased to 330 seconds on the second day after administration These changes unexplained at present support the necessity of the simultaneous administration of heparin in therapy

Discussion

In addition to pathologic changes in the vessels another factor producing thrombosis in atherosclerosis is the failure of function of the physiologic anticoagulant system heparin and fibrinolysin [1 10] A possible explanation for the tendency to thrombosis in atherosclerosis is the decrease in the content of heparin and fibrinolysin in the blood [2 4 6 11 1] The anatomic changes in the vessels may influence the production of anticoagulants and thrombolytic agents It is known that the formation of heparin is accomplished by mast cells and that the fibrinolytic activity of blood depends on the vascular wall Our observations suggest that an increase in the activity of agents counteracting heparin and fibrinolysin may be another factor in the pathogenesis of thrombosis in atherosclerosis There is a progressive increase in the activity of these inhibitory agents with progression of the disease They may be connected with lipid metabolism particularly the change in lipoprotein content observed by Greig and Runde De Leon and associates and Tsitouris and associates[14] attach great importance to the increase in antifibrinolytic activity of blood as a pathogenic factor in thrombosis We do not consider this to be the only factor but it may play a role in the complex pathogenic mechanism The change in the activity of antifibrinolysin may alter the efficacy of therapy with fibrinolysin The activity of antiheparin and antifibrinolysin decreases during therapy with heparin and fibrinolysin However on the second day the inhibitory activity increases necessitating repeated administration of fibrinolysin

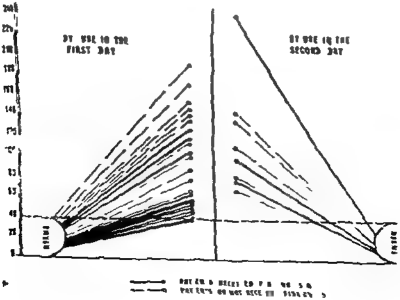

Fig 1 Transaminase level of blood in ... with myocardial infarction.

Summary

1. The activity of antiheparin and antifibrinolysin is increased during the development of atherosclerosis.

2. The increase in activity is one of the factors producing thrombosis in atherosclerosis.

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Optimum criteria for the diagnosis of patent ductus arteriosus from measurements of blood oxygen saturation

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The diagnosis of patent ductus arteriosus (PDA) is often made with a high degree of confidence when the murmur is of the classic variety and the clinical findings are consistent with the diagnosis. Indeed, the foregoing is frequently a sufficient basis for the recommendation that surgery be performed. However, in many instances the auscultatory findings leave uncertainty in the diagnosis such that laboratory examination is deemed to be necessary. Such instances include, for example, patients with PDA in whom the murmur is of systolic timing only, and patients in whom other causes of continuous murmurs are considered, such as coronary A-V fistula, peripheral pulmonary artery stenosis, or ventricular septal defect with a displaced aortic valve leaflet.

Since present-day therapy favors the operative repair of all small PDAs, it is essential to verify or exclude the diagnosis of PDA whenever it is entertained. Yet it is in the very situation of uncertainty when cardiac catheterization is required to clarify the diagnosis that we have found current diagnostic criteria based upon measurement of blood oxygen wanting in accuracy. Depending upon the criterion employed, either some small shunts were not detected (insensitive test) or the criteria were fulfilled in some patients who had no shunt (unreliable test). Therefore we sought to determine whether more accurate criteria could be formulated employing the approach of mathematical statistics. It is an inherent property of this procedure that no better use of the data is possible for the purpose of deciding whether a shunt exists.

In application of the statistical method two hypotheses are formulated: (1) The shunt *does not* exist. This is the "null" hypothesis, a designation which indicates that no increment in blood oxygen existed to suggest the presence of a contaminating stream. (2) The shunt *does* exist. This is the alternate hypothesis. One or the other hypothesis must be true. However, to form a basis for decision, the

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Table I. General classification system

Group	
I	No shunt
One shunt	
II	Ventricular septal defect
III	Patent ductus or other great vessel communication
IV	Atrial septal defect
Two or more shunts	
V	Ventricular septal defect and great vessel communication
VI	Atrial septal defect and patent ductus
VII	Atrial septal defect and ventricular septal defect
VIII	Other combinations
IX	Incomplete evaluation

Table II. Classification of 63 patients without any shunt (Group I)

Subgroup		Number
IA	No murmur	2
IB	Functional murmur	30
IC	Pulmonary stenosis	17
ID	Aortic stenosis	6
IE	Aortic insufficiency	2
IF	Mitral stenosis	2
IG	Mitral insufficiency	4
	Total	63

distribution of blood oxygen measurements or a statistic thereof is determined both in a group of patients *without* the shunt and a group *with* the shunt. Then from the respective distributions of the statistic in these two groups a boundary can be selected which provides optimum separation of the two if separation is possible. On one side of the boundary is the region containing principally values from patients without the shunt; this is called the *noncritical region* and corresponds to acceptance of the null hypothesis. On the other side of the boundary is the region containing principally values from patients with the shunt; this is called the *critical region* and corresponds to rejection of the null hypothesis and therefore acceptance of the alternate hypothesis. It is of great value that, for the boundary selected, the percentage of statistical values from the group without a shunt which fell in the critical region is known, and this provides immediate information as to the incidence of false positive diagnoses. Similarly, the percentage of statistical values from the patients with the shunt which fell into the noncritical region is known and this is the incidence of false negative diagnoses.

For the purpose of this study *reliability* and *sensitivity* are defined as follows. Reliability is the probability of correctly excluding a shunt. Thus a reliability error is a false positive diagnosis (Type I error). Denoting the probability of a false positive decision by P(fp), we define an Index of Reliability = 1.0 − P(fp).

Sensitivity is the probability of diagnosing an existing shunt. Thus a sensitivity error is a false negative diagnosis (Type II error). Denoting the probability of a false negative decision by P(fn), we define an Index of Sensitivity = 1.0 − P(fn).

This report presents the data pertinent to the application of the above described statistical approach to PDA with left to right shunt, derives from these data an optimum* diagnostic criterion for this shunt from measurements of blood oxygen saturation, and compares this criterion with others commonly in use today.

Material

During an 18 month period, 257 consecutive catheterizations of the right side of the heart were performed. Each patient studied was evaluated by a combination of physical examination, x-ray film and fluoroscopy, electrocardiography, vectorcardiography, and cardiac catheterization with oxygen analyses. Hydrogen indicator dilution curves,[8] selective angiocardiography, surgical confirmation, or postmortem examination were available in most cases. All 257 patients without exception were grouped according to the type and number of shunts present (Table I). Thus no selection of cases occurred once the patient had been referred for cardiac catheterization.

Group I. This group consists of 63 patients without a shunt as determined from the evaluation described above (Table II).

*An opt[illegible] [illegible] is defined as that [illegible] which [illegible] mize the total [illegible] of false p[illegible] and [illegible] error

In 60 cases independent laboratory or anatomic corroboration was available from hydrogen indicator dilution curves, selective angiocardiography, surgery, or post mortem examination. No such corroboration was available in 1 patient with pure valvular pulmonary stenosis and in 2 females with rheumatic mitral stenosis. (For details of laboratory and anatomic data see Reference 2, Table II.)

Group III. PDA as an isolated communication was present in 16 patients. Confirmation was available in all these cases as follows: surgical division 9, postmortem examination 2, angiography 2, hydrogen indicator dilution curves 3. Two of the patients operated on underwent simultaneous open repair of subaortic stenosis.

Method

The following sampling procedure was employed: the catheter was first manipulated into the central pulmonary arterial tree and at least three specimens of blood were obtained at different points therein. Additional specimens from the left or main pulmonary arteries were obtained if a small PDA was suspected. During withdrawal of the catheter, the following minimum number of samples was successively obtained in rapid sequence: 4 samples from the right ventricular outflow tract (2 immediately beneath the pulmonary valve and 2 lower in the vicinity of the crista supraventricularis), 4 samples from different points within the central or low central regions of the right atrium, 2 samples from the superior vena cava, and 3 samples from different points within the high inferior vena cava. A more detailed account of this sampling technique has been given previously.[2]

In each patient, spectrophotometric measurements of blood oxygen saturation were grouped according to the five anatomic locations mentioned above. For each location, the group mean (average) was calculated, the deviation of each value from the mean was squared, and the squares were summed. The difference in means between the pulmonary artery and the right ventricular outflow tract was standardized by dividing this difference by the estimated standard deviation. This estimate is based upon the sum of squares and the number of measurements from the pulmonary artery and right ventricular groups, respectively, in the particular patient. Thus the data in each patient provide their own estimate of the standard deviation for the particular difference being examined. The difference in means so standardized is the t statistic and in this case represents the number of estimated standard deviations by which the measured oxygen saturation within the pulmonary artery exceeds that within the right ventricular outflow tract. Illustrative examples of the grouping and calculation are shown in the Appendix.

The level of significance of each t statistic was determined from a table of the *cumulative t distribution*. Such a table gives the location of t in terms of the fraction of the area beneath the ideal distribution curve which lies to the right of the particular value of t. This area is referred to as the *level of significance* and represents the probability of obtaining a value greater than t by chance alone in the absence of the shunt. This table and its use with the illustrative examples is shown in the Appendix.

Results

The distribution of t in patients with no shunt and in patients with a left to right shunt through a PDA alone is shown in Fig. 1. The optimum experimental separation of the noncritical and critical regions was provided by that value of t corresponding to the 1 per cent level of significance. The critical region lies to the right of this value and is the region occupied by the 1 per cent right hand tail area of the theoretical t-distribution curve for differences in oxygen saturation between pulmonary artery and right ventricle in patients without any shunt.

Group I. Of the 63 studies in patients without a shunt, one study did not provide acceptable data because of the onset of atrial flutter-fibrillation during the sampling of blood from the main pulmonary artery prior to withdrawal across the pulmonary valve. This arrhythmia did not subside until after the catheterization was terminated.

Of the 62 acceptable compariso[illegible]
pulmonary artery [illegible]

of 0 5 volume per cent within the pulmonary artery was fulfilled in 18 studies a 29 per cent incidence of false positive tests and a complementary reliability of 71 per cent This far exceeds a tolerable incidence of the false positive error The criterion of 0 5 volume per cent is too lenient and therefore this criterion is considered not to be useful This judgment is not mitigated by the fact that all 16 patients with a PDA fulfilled the criterion for this only reflects the ease with which the criterion is met

The criterion of an increment of 0 8 volume per cent within the pulmonary artery being stricter than the former one was fulfilled in only 4 of our 62 studies in patients without a shunt This is a 6 5 per cent incidence of false positive tests and the complement reliability is 93 5 per cent Of our 16 patients with PDA 3 did not demonstrate an increment of 0 8 volume per cent which is a 19 per cent incidence of false negative results and a complementary sensitivity of 81 per cent Therefore the criterion of an increment of 0 8 volume per cent was [illegible]y as reliable as our criteria employing the t distribution but was moderately less sensitive smaller shunts not being recognized

The availability of photometric methods for determining blood oxygen saturation prompted the redefinition of criteria for shunts based upon such measurements rather than the absolute oxygen content of whole blood A method of withdrawing samples of blood in rapid succession through a cuvette oximeter provided data in 26 subjects who had no demonstrable shunt [5] Of these only 9 subjects were employed in the determination of criteria for a left to right shunt through a PDA The authors offer the criterion that an increment in saturation of 2 percentage points which exists uniformly between paired respective specimens from right ventricle and pulmonary artery is diagnostic of a left to right shunt into the pulmonary artery

We evaluated this criterion from our data by pairing measurements from the pulmonary artery and right ventricle in all possible combinations of two In 62 cases without any shunt the criterion of a saturation increment of 2 percentage points was unequivocally met in 7 cases an 11 per cent incidence of false positive results and a complementary reliability of 89 per cent

In 16 patients with proved patent ductus arteriosus carrying a left to right shunt a uniform difference of 2 percentage points between pulmonary artery and right ventricular outflow tract occurred in 13 instances providing a sensitivity of 81 per cent Therefore in our group of patients the criterion of a uniform 2 per cent increment in oxygen saturation within the pulmonary artery was less reliable and less sensitive than criteria based upon the t distribution

Multiple shunts The criteria of the present study and those others discussed above were based upon data in patients without any shunts in which cases the right ventricle contained only mixed venous blood for comparison with measurements in the pulmonary artery Therefore these criteria should be considered not to be similarly applicable to the diagnosis of a patent ductus which is preceded by another left to right shunt since the latter may result in a distinctly different distribution of oxygen saturation measurements within the right ventricle

Summary and conclusions

An over all evaluation of 259 consecutive patients undergoing catheterization of the right side of the heart yielded 63 studies of patients without any shunt and 16 cases of patent ductus arteriosus as an isolated left to right shunt Specimens of blood were obtained in rapid sequence and oxygen saturation was determined spectrophotometrically

In each case the difference between average saturation in the pulmonary artery and that in the right ventricular outflow tract was standardized with the standard deviation estimated from the respective data This standardized difference of means represents the number of estimated standard deviations by which the measured oxygen saturation within the pulmonary artery exceeds that within the right ventricular outflow tract The statistical significance of each difference was determined from the t distribution

When the 1 per cent level of significance was chosen as critical the method was 93 5 per cent reliable in excluding a shunt into the pulmonary artery and 94 per cent sensitive in the diagnosis of PDA with left to right shunt If a small shunt is suspected the sensitivity of the test is increased by obtaining additional specimens while the reliability of the test is unchanged providing the critical level of significance is kept at 1 per cent

It is concluded that for the diagnosis of a left to right shunt through a PDA from blood oxygen measurements criteria based upon the t-distribution are superior to other criteria previously described and currently in use The t test and associated criteria are easy to apply and together with blood oxygen data acquired by rapid sequential sampling provide an accurate method for the diagnosis of PDA with left to right shunt

Appendix

N_p = Number of specimens of blood from the pulmonary artery

N_v = Number of specimens of blood from the right ventricular outflow tract

P_i = Measured oxygen saturation within the pulmonary artery $i = 1, 2, \ldots N_p$

V_i = Measured oxygen saturation within the right ventricular outflow tract $i = 1, 2, \ldots N_v$

$\bar{P}$ = Mean oxygen saturation of specimens of pulmonary arterial blood

$\bar{V}$ = Mean oxygen saturation of specimens of blood from the right ventricular outflow tract

$$t = (\bar{P} - \bar{V}) \sqrt{\frac{(N_p + N_v - 2)}{\sum_{1}^{N_p} (P_i - \bar{P})^2 + \sum_{1}^{N_v} (V_i - \bar{V})^2} \times \frac{N_p \times N_v}{(N_p + N_v)}}$$

The value of t is the number of estimated standard deviations by which the difference of means $\bar{P} - \bar{V}$ lies from the hypothetical difference of zero in a patient without a shunt The significance of t is determined from a table of the cumulative t distribution

Cumulative t distribution

Degrees of freedom	Probability of a deviation greater than t			
	0 05 (5%)	0 025 (2½%)	0 01 (1%)	0 005 (½%)
4	2 13	2 78	3 75	4 60
5	2 02	2 57	3 37	4 03
6	1 94	2 45	3 14	3 71
7	1 90	2 37	3 00	3 50
8	1 86	2 30	2 90	3 36
9	1 83	2 2[illegible]	2 8[illegible]	3 25
10	1 81	2 [illegible]	[illegible] 6	3 17

*[illegible]

Example No. 1

Pulmonary artery

i	P	$P - \bar{P}$	$(P - \bar{P})^2$
#1	80.9	+0.7	0.49
#2	78.1	−2.1	4.41
#3	81.5	+1.3	1.69
$\bar{P} =$	80.2		6.59

$N_P = 3$

$\bar{P} = 80.2$

$$\sum_{1}^{N_P} (P - \bar{P})^2 = 6.59$$

Right ventricular outflow tract

i	I	$I - \bar{I}$	$(I_i - \bar{I})^2$
#1	77.9	+0.6	0.36
#2	76.1	−1.2	1.44
#3	77.9	+0.6	0.36
#4	77.2	−0.1	0.01
$\bar{I} =$	77.3		2.17

$N_I = 4$

$\bar{I} = 77.3$

$$\sum_{1}^{N_I} (I - \bar{I})^2 = 2.17$$

$$t = (80.2 - 77.3)\sqrt{\frac{(3 + 4 - 2)}{(6.59 + 2.17)} \cdot \frac{3 \times 4}{(3 + 4)}} = 2.9\sqrt{\frac{5 \times 3 \times 4}{8.76 \times 7}} = 2.87$$

Example No. 1. Degrees of Freedom $= (N_P + N_I - 2) = (3 + 4 - 2) = 5$. From the table of the cumulative t distribution use the horizontal line of values for five degrees of freedom. The calculated t is 2.87, which is greater than 2.57 (the $2\frac{1}{2}$ per cent value) but less than 3.37 (the 1 per cent value). Therefore, this value of $t = 2.87$ is significant at the $2\frac{1}{2}$ per cent level but not significant at the 1 per cent level.

Example No. 2

Pulmonary artery

i	P	$P - \bar{P}$	$(P - \bar{P})^2$
#1	78.1	−2.4	5.76
2	83.9	+3.4	11.56
3	80.4	−0.1	0.01
4	79.6	−0.9	0.81
5	79.9	−0.6	0.36
6	81.2	+0.7	0.49
$\bar{P} =$	80.5		18.99

$N_P = 6$

$\bar{P} = 80.5$

$$\sum_{1}^{N_P} (P - \bar{P})^2 = 18.99$$

Right ventricular outflow tract

i	I	$I - \bar{I}$	$(I - \bar{I})^2$
#1	77.3	+0.2	0.04
2	77.8	+0.7	0.49
3	76.1	−1.0	1.00
4	77.0	−0.1	0.01
$\bar{I} =$	77.1		1.54

$N_I = 4$

$\bar{I} = 77.1$

$$\sum_{1}^{N_I} (I - \bar{I})^2 = 1.54$$

$$t = (80.5 - 77.1)\sqrt{\frac{(6+4-2)}{(18.99+1.54)} \cdot \frac{6 \times 4}{(6+4)}} = 3.4\sqrt{\frac{8 \times 6 \times 4}{20.53 \times 10}} = 3.29$$

Example No 2 Degrees of Freedom = ($N_p + N - 2$) = ($6 + 4 - 2$) = 8 From the table of the cumulative *t*-distribution use the horizontal line of values for eight degrees of freedom The calculated *t* is 3 29 which is greater than 2 90 (the 1 per cent value) and is therefore significant at the 1 per cent level Note that $t = 3.29$ is almost as far to the right as the ½ per cent value 3 36

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Pharmacodynamic effects of alpha-methyl dopa in hypertensive subjects

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The sequence of reactions leading to the biosynthesis of norepinephrine proceeds at least in part from the conversion of dihydroxyphenylalanine (dopa) dopamine to norepinephrine[1] In 1938 tz[4] demonstrated in vitro and subsequently in vivo that the enzyme dopa decarboxylase catalyzes the decarboxylation of dopa to dopamine It is now evident that this same enzyme is responsible for the decarboxylation of other aromatic amino acids (including 5 hydroxytryptophan) and is active in the formation of other catecholamines (including 5 hydroxytryptamine)

It has been demonstrated that various compounds which affect the biosynthesis and metabolism of catecholamines can produce an antihypertensive response Of the numerous compounds known to inhibit aromatic amino acid decarboxylation alpha methyl dopa (alpha methyl 3 4 dihydroxy d l phenylalanine) has received the most extensive pharmacologic trial[4-6] and has been found to possess definite antihypertensive abilities It is the purpose of the present paper to report the effect of alpha methyl dopa on cardiac output and renal hemodynamics in human subjects with essential hypertension

Method and materials

In order to evaluate the hemodynamic effects of alpha methyl dopa† the drug was administered intravenously to 11 hospitalized hypertensive patients All antihypertensive medications had been discontinued for 4 or more weeks prior to the hemodynamic studies and all patients were maintained on a regular (5 Gm of salt) diet

The hemodynamic studies were performed with the subjects in the fasting state except for hydration with 500 ml of tap water given 1 hour prior to the procedure Cardiac outputs were determined by the indicator dilution technique using indocyanine green and a Gilford densitometer Intra arterial blood pressures were recorded from the brachial artery with a Statham strain gauge transducer Pulse pressures and dye curves were recorded on a photographic oscillograph Renal blood flows were determined by para

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aminohippurate clearance and glomerular filtration rates were measured by inulin clearance The reported results in each case represent the average of three determinations all values corrected to 1 73 square meters of body surface area

Cardiac and renal hemodynamic studies were performed in 8 subjects who had rested for 45 minutes in the supine position on a standard tilt table In these cases cardiac and renal studies were synchronized with the cardiac outputs studies which were performed during the middle of each clearance period In 2 additional patients renal function alone was investigated and in 1 other subject, cardiac function alone was assessed After three determinations each subject was passively tilted 40 degrees upright, and the cardiac and renal studies were repeated in this position

After the control determinations alpha methyl dopa was administered in a single intravenous dose (either 2 0 or 2 5 Gm) In each instance the maximum hypotensive response occurred from 10 to 20 hours after administration of the drug and the cardiac and renal hemodynamic studies were repeated at this time again with the subjects both in the supine and tilted positions

Results

Supine response The hemodynamic findings in the supine position are recorded in Table I A significant reduction in blood pressure was observed in each subject after administration of the drug ($p < 0001$) but there were no consistent changes in pulse rate At the time of the maximum antihypertensive response the cardiac output was reduced in 7 of the 9 subjects (Patients 1 2 3 5 6 7 8) in the other 2 (Patients 4 9) an increase in cardiac output was observed The average reduction in cardiac output was [illegible] per cent ($p > 0 1$) The calculated total peripheral resistance decreased in all cases ($p < 0 01$)

During the hypotensive response the renal blood flow increased in 4 subjects (Patients 1 2 4 11) and decreased in the other 6 (Patients 3 5 6 7 9 10) The glomerular filtration rate increased or remained unchanged in 3 subjects (Patients 1 2 6) In the other 7 subjects the glomerular filtration rate diminished (Patients 4 5 7 9 10 11) The average reduction in renal blood flow was 8 per cent ($p > 0 1$) and the average decrease in glomerular filtration rate was 13 per cent ($p < 0 05$) In each instance the arterial blood pressure decreased proportionately more than the renal blood flow so that the calculated renal vascular resistance was consistently and significantly reduced ($p < 0 05$)

Erect response The hemodynamic findings in the erect position before and after the intravenous administration of alpha methyl dopa are recorded in Table II During the hypotensive response, the cardiac output was reduced in 5 of the 9 subjects (Patients 1 2 5 7 8) In the other 4 (Patients 3 4 6 9) an increase in cardiac output was observed The calculated total peripheral resistance decreased in all subjects except one (Patient 1) in the latter case the increased total peripheral resistance was accompanied by a substantial drop in cardiac output The over all average decrease in cardiac output was 8 per cent ($p > 0 1$) and the average reduction in total peripheral resistance was 32 per cent ($0 05 < p < 0 1$)

The renal blood flow increased in 5 subjects (Patients 1 2 4 10 11) and decreased in the other 5 (Patients 3 5 6 7 9) The glomerular filtration rate decreased in 5 (Patients 3 5 [illegible] 7 10) increased in 1 (Patient 2) and remained essentially unchanged in 4 (Patients 1 4 9 11) The changes in renal function over all were not statistically significant However in each instance the calculated renal vascular resistance was consistently and significantly reduced ($p < 0 05$)

Effect of tilting During the control studies (Table III) passive head up tilting produced inconsistent changes in the mean arterial blood pressure but the cardiac output diminished ($p < 0 05$) The latter response was generally compensated for by increased peripheral arteriolar resistance In 2 subjects however a decrease in total peripheral resistance in the erect position resulted in a significant reduction in orthostatic blood pressure (Patients 1 and 8) This faulty orthostatic mechanism after passive tilting occurs not [illegible] frequently in patients with essential hypertension [7] Renal blood flow and glomerular filtration tended to be lower whe

Table I Hemodynamic response after intravenous alpha methyl dopa (supine position)

Patient	MAP		CO		TPR	
	C	R	C	R	C	R
1 G D	123	109	5 40	4 94	1 820	1 764
2 J R	155	123	3 79	3 25	3 271	3 017
3 D G	138	104	4 93	4 50	2 238	1 847
4 W S	153	128	5 38	5 60	2 274	1 828
5 C R	156	116	6 98	5 78	1 786	1 604
6 C S	168	139	4 80	4 07	2 797	2 730
7 R W	144	102	5 24	5 05	2 197	1 615
8 I S	146	101	4 28	3 84	2 727	2 101
9 H M L	167	134	4 90	6 15	2 726	1 741
10 J M W	148	101	—	—	—	—
11 R B	123	88			—	—
Mean	147	113	5 08	4 80	2 426	2 034
% of Control		76		94		81
p Value		<0 001		>0 1		<0 01

C Control R Response to alpha methyl dopa MAP M n arterial blood pressure (mm Hg) CO Card c outp t (l t rs m) TPR blood fl w (c min) GFR Gl merula filtrat on te (inulin cle ce) (c /min) FF F ltration fraction RVR R nal v s

Table II Hemodynamic response after intravenous alpha methyl dopa (erect position)

Patient	MAP		CO		TPR	
	C	R	C	R	C	R
1 G D	106	100	5 30	3 55	1 606	2 253
2 J R	140	103	3 22	2 44	3 479	3 379
3 D G	145	81	3 41	3 70	2 795	1 751
4 W S	147	99	3 41	3 88	3 509	2 040
5 C R	176	84	6 44	4 58	3 904	1 465
6 C S	158	100	3 86	5 42	3 507	1 475
7 R W	147	91	5 40	4 05	2 175	1 795
8 I S	136	[illegible]	4 43	3 49	2 455	2 017
9 H M L	184	146	4 30	5 40	3 413	2 160
10 J M W	153	92	—	—	—	—
11 R B	118	70	—	—	—	—
Mean	146	95	4 41	4 06	2 987	2 037
% of Control		65		92		68
p Value		<0 001		>0 1		0 05<p<0 1

Abbreviations as in Table I

patients were in the upright position ($p < 0.01$) and renal vascular resistance showed an over all tendency to increase ($p < 0.05$)

The hemodynamic effects of passive head up tilting during the hypotensive response to alpha methyl dopa are recorded in Table IV Upright tilting caused a fall in mean arterial blood pressure in all sub jects except one ($p < 0.01$) and the cardiac output tended to diminish ($p < 0.05$) The calculated total peripheral resistance

RPF		RBF		GFR		FF		RVR	
C	R	C	R	C	R	C	R	C	R
472	489	813	843	74	78	0 16	[illegible] 16	11 06	9 05
391	421	674	725	73	78	0 19	0 19	17 14	12 41
467	349	833	623	67	52	0 13	0 15	17 24	11 65
301	309	537	551	58	56	0 [illegible]	0 18	21 20	17 22
690	61[illegible]	1 189	1 035	131	9[illegible]	0 19	0 16	9 78	7 99
96	[illegible]	177	167	16	16	0 17	0 18	71 11	63 43
488	424	873	757	78	57	0 16	0 13	13 21	9 68
406	350	712	614	76	56	[illegible] 19	0 16	17 56	16 09
386	313	584	474	62	52	0 16	0 17	18 85	15 28
350	381	614	668	60	58	0 17	0 15	13 4[illegible]	9 29
404	373 92 >0 1	700	647 9[illegible] >0 1	69	60 [illegible] <0 05	0 17	0 16 94 >0 1	20 56	17 20 84 <0 05

T tal periph ral res ta c (dy sec./cm 5) RPF Renal pl ma fl w (para am n hippurat cle rance) (c c. m n) RBF Renal enl en tance (dy sec./ m 5 × 10[3])

RPF		RBF		GFR		FF		RVR	
C	R	C	R	C	R	C	R	C	R
401	513	691	887	74	77	0 18	0 15	11 07	8 07
364	528	627	910	67	83	0 17	0 15	16 52	8 14
340	304	607	542	57	47	0 17	0 15	17 72	10 43
237	280	473	500	43	43	0 18	0 15	25 80	14 18
510	421	879	725	109	64	0 21	0 15	15 04	8 12
73	62	135	114	14	12	0 19	0 19	87 34	67 89
466	391	833	685	73	51	0 15	0 13	13 10	9 41
458	360	803	631	75	72	0 16	0 20	17 39	17 18
341	372	516	563	59	51	0 17	0 14	22 07	11 60
298	311	522	545	53	49	0 18	0 16	15 78	8 64
349	354 107 >0 1	603	610 107 >0 1	61	55 90 >0 1	0 17	0 16 94 >0 1	24 17	15 [illegible] 66 <0 05

increased with tilting in 5 subjects and decreased in the other 4 The renal blood flow increased in 4 subjects including 3 in whom tilting resulted in a fall in orthostatic blood pressure In the other 6 subjects the reduction in renal blood flow accompanied the reduction in orthostatic blood pressure Changes in glomerular filtration tended to be minor and inconsistent In contrast with the control studies however the reduction in blood pressure produced by tilting was accompanied

Table III Hemodynamic effect of head up tilting (control studies)

Patient	MAP		CO		TPR	
	S	E	S	E	S	E
1 G D	123	106	5 40	5 30	1 820	1 606
2 J R	155	140	3 79	3 22	3 271	3 473
3 D G	138	145	4 93	3 43	2 238	2 795
4 W S	153	147	5 38	3 41	2 274	3 503
5 C R	156	176	6 98	6 44	1 786	1 907
6 C S	168	158	4 80	3 86	2 497	3 507
7 F W	144	147	5 24	5 40	2 197	2 175
8 I S	146	136	4 28	4 43	2 727	2 455
9 H M L	164	184	4 90	4 30	2 426	3 413
10 J M W	148	153	—	—	—	—
11 R B	123	116	—	—	—	—
Mean	147	146	5 08	4 42	2 426	2 981
% of Control		100		87		123
p Value				<0 05		0 05<p<0 1

S Supine E Erect Other abbreviations as in Table I

Table IV Hemodynamic effect of head up tilting during the hypotensive response to alpha methyl dopa

Patient	MAP		CO		TPR	
	S	E	S	E	S	E
1 G D	109	100	4 94	3 55	1 766	2 253
2 J R	123	103	3 25	2 44	3 077	3 379
3 D G	104	[illegible]	4 50	3 70	1 847	1 751
4 W S	128	99	5 60	3 88	1 828	2 040
5 C R	116	84	5 78	4 58	1 604	1 466
6 C S	139	100	4 07	5 47	2 730	1 475
7 R W	102	91	5 05	4 05	1 615	1 795
8 I S	101	[illegible]	3 84	3 49	2 101	2 017
9 H M L	134	146	6 15	5 40	1 741	2 160
10 J M W	101	92	—	—	—	—
11 R B	88	70	—	—	—	—
Mean	113	95	4 80	4 06	2 034	2 037
% of Control		84		85		100 1
p Value		<0 01		<0 [illegible]		

S Supine E Erect Other abbreviations as in Table I

a significant decrease in renal vascular resistance (p < 0 05)

Discussion

The hemodynamic studies performed with intravenous alpha methyl dopa suggest that the drug lowers blood pressure primarily by peripheral arteriolar relaxation Although there was an accompanying decrease in cardiac output in the majority of cases the latter response was not consistent In those instances in which the cardiac output did diminish however the anticipated reflex arteriolar constriction (which under normal circumstances minimizes a fall in blood pressure when cardiac

RPF		*RBF*		*GFR*		*FF*		*RVR*	
S	*E*	*S*	*E*	*S*	*E*	*S*	*E*	*S*	*E*
477	401	813	691	74	74	0 16	0 18	11 06	11 07
391	364	674	677	43	67	0 19	0 17	17 14	16 57
467	340	833	607	62	57	0 13	0 17	12 24	17 77
301	237	534	423	58	43	0 19	0 18	21 20	25 80
690	510	1 129	879	131	109	0 19	0 21	9 78	15 04
96	73	177	135	16	14	0 17	0 19	71 11	87 34
488	466	873	833	78	73	0 16	0 16	13 21	13 10
—	—	—	—	—	—	—	—	—	—
406	458	512	803	76	75	0 19	0 16	17 56	17 39
386	341	584	516	67	59	0 16	0 17	18 [illegible]	22 07
350	298	614	522	60	53	0 17	0 18	13 47	15 78
404	348 86 <0 01	694	603 86 <0 01	69	61 88 <0 01	0 17	0 17 100	20 56	24 17 115 <0 05

RPF		*RBF*		*GFR*		*FF*		*RVR*	
S	E	*S*	E	*S*	E	*S*	E	*S*	E
489	513	843	887	78	77	0 16	0 15	9 05	8 07
471	528	775	910	78	83	0 19	0 15	12 41	8 14
349	304	673	512	52	47	0 15	0 15	11 65	10 43
309	280	551	500	56	43	0 18	0 13	17 22	14 18
612	471	1 055	725	97	64	0 16	0 15	7 99	8 12
88	62	162	114	16	12	0 18	0 19	63 43	67 89
474	391	757	685	57	51	0 13	0 13	9 68	9 91
—	—	—	—	—	—	—	—	—	—
350	360	614	631	56	72	0 16	0 20	16 09	17 18
313	372	474	563	57	51	0 17	0 14	15 28	11 60
381	311	668	545	58	49	0 15	0 16	9 29	8 64
373	354 95 >0 1	647	610 95 >0 1	60	55 97 >0 1	0 16	0 16 100	17 20	15 86 92 <0 05

output is decreased) appears to have been prevented or at least reduced by alpha methyl dopa The inconsistent and probably insignificant effect of the drug on cardiac output is emphasized in Tables III and IV which compare the effect of tilting on blood pressure during control studies and during the administration of alpha methyl dopa In both instances the cardiac response to tilting was essentially the same i e and approximate 15 per cent reduction in cardiac output In contrast whereas peripheral vascular resistance increased in the control studies (Table III) there was no significant percentage change in peripheral vascular resistan

during the hypotensive response to alpha methyl dopa (Table IV) Sannerstedt and associates[8] investigated the hemodynamic response to alpha methyl dopa during exercise Their studies also suggested that the hypotensive response to the drug is due *mainly to peripheral arteriolar relaxation* and that the effect on cardiac output is inconsistent

It is notable that despite a significant reduction in blood pressure renal blood flow increased in 4 of 10 patients in the supine position and in 5 of 10 in the erect position A moderate reduction in renal blood flow occurred in the other patients In each instance however renal vascular resistance was consistently reduced These findings suggest a favorable action of alpha methyl dopa on the renal arterial circulation It is of interest in this regard that the enzyme dopa decarboxylase is found in high concentration in the renal parenchyma[2,9]

The present studies indicate that intravenous alpha methyl dopa does indeed possess significant antihypertensive properties Although a greater orthostatic antihypertensive effect was achieved a significant reduction in blood pressure occurred in all cases in the supine position as well In general the disparity between supine and erect blood pressure responses was less than that observed with guanethidine and the ganglioplegic drugs

The hemodynamic response after the acute administration of alpha methyl dopa differs significantly from that obtained with guanethidine[10] The hypotensive effect produced by the latter drug appears to be due primarily to a reduction in cardiac output with minor effect on peripheral vascular resistance Renal blood flow and glomerular filtration are consistently reduced whereas the renal vascular resistance is increased or else little changed Consequently the renal hemodynamic response after the acute administration of guanethidine tends to be detrimental In contrast alpha methyl dopa tends to exert a beneficial effect on renal hemodynamics especially its consistent reduction in renal vascular resistance thereby suggesting potential usefulness of the drug in hypertensive patients with renal functional impairment

The ideal antihypertensive drug from a hemodynamic standpoint is not yet available Such a compound should be universally effective and equally active in both the supine and erect positions should have a predominant arteriolar *relaxant action* and should not compromise blood flow to the vital organs or decrease cardiac output

Summary

The decarboxylase inhibitor alpha methyl dopa is a potent antihypertensive agent The hypotensive action of the drug *appears to be due primarily to peripheral* arteriolar relaxation Its ability to reduce renal vascular resistance suggests its potential usefulness in the hypertensive patient with renal functional impairment

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Effects of age and heart disease on the QRS axis during the seventh through the tenth decades

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The purpose of the present study is to evaluate the effects of age on the QRS axis in patients free of clinical heart disease during the seventh through the tenth decades and to compare the findings with those in patients of the same age range with heart disease. The studies of Simonson[1] and of Hiss, Lamb, and Allen on large numbers of subjects carefully screened to exclude heart disease show that in health with increasing age from the third through the sixth decades there is a leftward trend of the frontal plane QRS axis. Whether this trend continues into old age has not been investigated previously in a comparable way.

Material and methods

The mean frontal plane QRS axis of 658 patients between 60 and 94 years of age was obtained[3] to the nearest 15 degrees from hospital electrocardiograms. There were 313 (48 per cent) males and 345 (52 per cent) females. Clinical information was obtained from the routine data filed with the electrocardiograms and the minimum required for inclusion in the study was as follows: age, blood pressure, digitalis or quinidine therapy, and clinical diagnosis or relevant symptoms or signs. The electrocardiograms were divided into those of patients without clinical heart disease, Group I, and those of patients with heart disease, Group II. There were 308 patients in Group I, consisting of 154 (50 per cent) males and 154 (50 per cent) females; the total in Group II was 350, with 159 (45 per cent) males and 191 (55 per cent) females.

The criterion for admission to Group I was absence of cardiovascular disease. Patients with the following clinical features were excluded from this group: history of dyspnea, chest pain, edema, syncope, or

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other symptoms of possible cardiac or pulmonary origin, blood pressure over 150 mm Hg systolic or 90 mm Hg diastolic, peripheral or cerebral occlusive vascular disease, diabetes mellitus, or any condition frequently associated with cardiopulmonary disease. Among electrocardiographic grounds for exclusion from this group were the presence of bundle branch block, myocardial infarction, QRS-T angle greater

*Table I. Percentage distribution of mean frontal plane QRS axis according to age and the presence or absence of heart disease in 655 patients**

Mean frontal plane QRS axis (degrees)	Age in 5 year subgroups (Group I, No heart disease; Group II, Heart disease): 60-64		65-69		70-74		75-79		80-84		85-89		90-94	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
-90								2						
75			2	2										
60	2	6		2		4						8		10
45	2		2	4	6	6	4	2	4	6	3	6	8	16
30	8	12	4	12	10	10	6	4	8	14	9	12		16
-15	6	12	4	12	12	16	20	6	12	18	6	14	16	18
0	12	16	18	30	12	12	24	32	22	22	18.5	24	16	22
15	14	12	20	8	14	8	12	18	6	10	9	4	8	8
30	24	10	20	10	18	20	22	16	16	16	15	16	16	6
45	10	8	14	8	14	4	4	6	20	4	18.5	8	8	2
60	18	16	10	12	8	10	6	10	8	8	12	8	16	2
75	4	8	6		6	8	2	2	2		9		12	
90						2			2	2				
105								2						

Percentages in Groups I and II for each 5 year subgroup are based on 50 patients except in Group I 85-89 years (33 patients) and Group I 90-94 years (25 patients).

Table II

Age group	Group I, No heart disease: Patients: Number	Sex: M (%)	F (%)	QRS axis (in degrees): Mean	S.D.	Quartiles: 1	2	3	Group II, Heart disease: Patients: Number	Sex: M (%)	F (%)	QRS axis (in degrees): Mean	S.D.	Quartiles: 1	2	3
60-64	50	40	60	22.2	32.4	0	30	45	50	44	56	15.0	38.2	-15	15	45
65-69	50	48	52	21.6	30.9	0	15	45	50	44	56	5.1	33.1	-15	0	30
70-74	50	56	44	15.6	33.5	-15	15	45	50	38	62	12.3	39.0	-15	15	30
75-79	50	36	64	8.7	27.5	-15	0	30	50	42	58	15.0	37.4	0	15	30
80-84	50	60	40	16.8	32.3	0	15	45	50	30	70	5.1	31.3	-15	0	30
85-89	33	67	33	23.2	33.6	0	30	45	50	54	46	0.6	34.3	-30	0	30
90-94	25	48	52	22.2	36.5	0	30	60	50	66	34	-15.6	28.7	-45	-15	0

*Median

†S.D., standard deviation

than 90 degrees in the frontal plane and arrhythmias other than those of sinus origin however patients with sinus tachycardia faster than 120 per minute were not included

The criterion for admission to Group II was the presence of cardiovascular disease whether symptomatic or not Patients with diastolic pressures of 100 mm Hg or higher were included Electrocardiographic findings leading to exclusion from this group were bundle branch block and arrhythmias whenever they interfered with calculation of the QRS axis or when the ventricular rate was greater than 120 per minute

Data from consecutive patients who met the above mentioned criteria were collected until each 5 year subgroup in both main groups contained 50 patients When any subgroup was complete the search was narrowed to the remaining unfilled subgroups It was not possible within the time allotted to the study to complete the last two subgroups in Group I for which we could obtain only 33 and 25 patients respectively

In this study the group of patients free of heart disease according to the information utilized and the criteria described may contain a number of patients with minor or unrecognized heart disease but it is assumed that the proportion of these will not vary significantly with age so that the method is valid for investigating trends if not absolute ranges of normality On account of this differences between the disease and nondisease groups would tend to be reduced any significance in such differences would therefore be enhanced

It is well known that habitus affects the direction of the QRS axis This was not taken into account in the present study since normal ranges of height and weight have not been established beyond the seventh decade

Since the path of depolarization is abnormal in bundle branch block the QRS axis direction will not be comparable with that of patients without such conduction defects This consideration determined the exclusion of patients with such abnormalities from the heart disease group

All types of heart disease were included in Group II Some subjects had involvement of the right ventricle from congestive heart failure and some had dominant right ventricular involvement as in cor pulmonale or pulmonary embolism The inclusion of the latter conditions in Group II will tend to reduce differences between the disease and nondisease groups with respect to QRS axis direction since these conditions tend to shift the axis to the right

Determinations of individual QRS axis direction were made to the nearest 15 degrees in accordance with the view that this is the limit of accuracy obtainable from records taken by standard electrocardiographic technique

Results

The percentage distribution of the mean frontal plane QRS axis to the nearest 15 degrees according to age and the presence or absence of heart disease is shown in Table I As shown in Fig 1 the proportion with left axis deviation of −30 degrees or

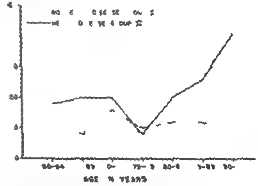

Fig 1 Percentage of patients with left axis deviation of −30 degrees or greater according to age and the presence or absence of heart disease

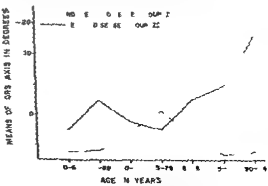

Fig 2 Means of QRS axis according to age and the presence or absence of heart disease

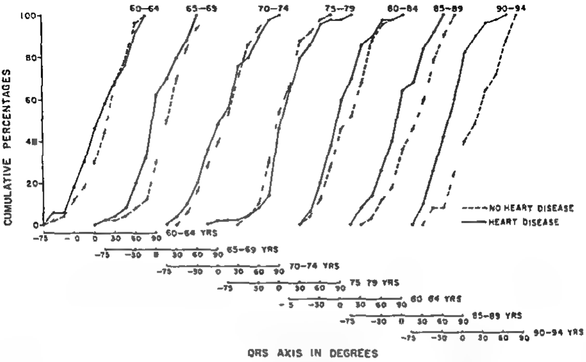

Fig. 3. Cumulative percentage distributions of the QRS axis according to age and the presence or absence of heart disease. The cumulative per cent is the per cent of patients in a group which has a given QRS axis or a value leftward of this on the hexaxial system. There is a common ordinate for the cumulative percentage and separate abscissa for each 5 year age period.

greater is higher in those with heart disease than in those without it in the seventh, ninth, and tenth decades; the difference is particularly marked in the last two decades.

The sex distribution, means, standard deviations, and quartiles of the QRS axis are given in Table II. As shown in Fig. 2, the means of the QRS axis show no clear trend with age in those without heart disease. In those with heart disease the means of the QRS axis during the seventh decade show a slight leftward trend and during the ninth and tenth decades a marked leftward trend. The early tendency to the left is interrupted in the eighth decade by a moderate shift to the right. At the 85 to 89 and 90 to 94 year age levels the differences between the means in both groups of patients are significant at the .01 level with the "t" test.*

The cumulative percentage distributions of the QRS axis according to age and the presence or absence of heart disease as shown in Fig. 3 demonstrate the striking differences at the two upper age levels.

Subdivision into males and females did not yield any further information of value.

Discussion

The smaller numbers of cases in the last two 5 year subgroups of patients without clinical heart disease reflect the difficulty in finding such patients in the ninth and tenth decades. Despite the discrepancy in size between these and the subgroups of patients with heart disease at this age level, the "t" test for statistical significance can be applied since the standard deviations (see Table II) are comparable.

Grant[4] showed in an electrocardiographic pathologic study that left axis deviation of −30 degrees or greater is usually a manifestation of underlying left ventricular disease. Our finding that a tendency to left axis deviation occurs in the patients with clinical heart disease but not in those without it is in agreement with this and also suggests that aging alone is not a significant factor in the production of left axis deviation of this degree.

*The distribution of the QRS axis were essentially normal and this allowed use of statistical formula based on the normal distribution curve.

Summary

The mean frontal plane QRS axis of 658 patients between 60 and 94 years of age was obtained 313 (48 per cent) were males and 345 (52 per cent) were females There were 308 patients without cardiovascular disease (Group I) and 350 patients with cardiovascular disease (Group II) These were divided by age into 5 year sub group

In Group I the mean of the QRS axis showed no significant trend to the left with age whereas in Group II there was a marked leftward trend in the ninth and the tenth decades In the last three 5 year sub groups the means of the frontal plane QRS axis in Group I were 16 8 23 2 and 22 2 degrees respectively and corresponding values in Group II were 5 1 0 6 and −15 6 degrees The differences between the means in the last two subgroups are statistically significant

The proportion with left axis deviation (−30 degrees or above) was greater in Group II than in Group I particularly in the last two 5 year subgroups The percentages were as follows Group II 26 and 42 Group I 12 and 8

Conclusion

The findings of this study suggest that aging alone is not a significant factor in the production of left axis deviation of −30 degrees or greater and that left axis deviation of this extent is usually due to heart disease

We are grateful to Dr C B Ethridge Dr J M Evans and Dr H H Orvis for their criticisms We appreciate the cooperation of Dr C L Miller and Miss M Camut of the Soldiers Home Washington D C and of Dr R A Masumi of the District of Columbia General Hospital in making records available

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Experimental and laboratory reports

Correlations between radiologic heart size and orthogonal electrocardiograms in patients with left ventricular overload

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Correlations between heart size and electrocardiograms have always stimulated considerable interest because both of these measurements are almost routinely performed in cardiac practice. It is generally recognized that the estimation of heart size by physical examination is frequently unreliable and that the determination of heart size radiologically is therefore commonly preferred. It has to be recognized, however, that radiologic heart size is not a true measure of cardiac hypertrophy or dilatation because such conditions can be found in varying combinations with radiologic enlargement of the cardiac shadow. In both instances left ventricular overload (LVO) can be assumed to be present. This term, LVO, appears to be preferable, therefore, when radiologic enlargement is found.

In most reported correlations[1-7] a common difficulty was the undesirable large percentage of instances of false positive and false negative electrocardiographic findings. Therefore, in the present study an attempt was made to search for optimal electrocardiographic parameters indicating radiologic cardiac enlargement in LVO but keeping false positive and false negative rates at an absolute minimum. A digital computer was used for this extensive search.

Material and methods

One hundred male patients who ranged in age from 27 to 79 years were available for the study. All subjects had clinical evidence of LVO, including 85 patients with sustained diastolic hypertension (above 100 mm. Hg), 3 patients with aortic stenosis, 8 patients with aortic insufficiency, and 4 patients with mixed aortic valve lesions. Patients with a history of coronary artery disease or electrocardiographic evidence of ventricular conduction defect (QRS duration exceeding 0.12 second) were excluded. One or more posteroanterior chest films were available for each subject. The radiologic heart size was expressed as per cent deviation of the maximum transverse diameter from predicted values for weight and height according to Ungerleider and Gubner.[8] The reason for employing this method was mainly its widespread use and simplicity of application.

According to their radiologic heart size the subjects were classified into three

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groups Group A included 34 patients with a heart size of +10 per cent or less Group B included 25 patients with a heart size of +11 to 20 per cent Group C included 41 patients with a heart size of 21 per cent or greater The patients of Group A were assumed to have normal heart size whereas those of Groups B and C were considered to have radiologic evidence of cardiac enlargement A history of one or more episodes of left ventricular failure was present in 4 patients (12 per cent) of Group A 8 patients (32 per cent) of Group B and 26 patients (63 per cent) of Group C Digitalis was being used in 36 patients at the time of electrocardiographic recording

Frank s corrected orthogonal lead system[9] was used for electrocardiographic recording Chest electrodes were placed at the level of the fourth intercostal space as recommended for the supine position[10] The polarity in the three orthogonal leads was used as follows In lead X positive deflections indicated leftward direction and negative deflections indicated rightward direction in lead Y positivity indicated inferior direction and negativity indicated superior direction in lead Z positive polarity was used for indicating posterior direction and negative polarity for indicating anterior direction The three orthogonal leads were recorded simultaneously on magnetic analog tape using FM channels Voltages of each lead were digitized automatically at a sampling rate of 1 000 per second using an analog to-digital converter Subsequently they were fed into a digital computer (IBM 7090) for data processing and analysis Details of these procedures were reported previously[11]

The following electrocardiographic measurements of the QRS complex were selected for study because they were assumed to discriminate best between normal and LVO records (1) magnitude of Q waves in three scalar leads and the Q/R ratio in lead Z (2) magnitude of R waves in leads X and Z and the sum of these two (3) R/S ratio in lead Y (4) spatial magnitude and orientation of the time integral of QRS (SÂQRS) (5) spatial magnitude and orientation of the maximal QRS vector (6) spatial magnitude and orientation of instantaneous vectors at 0 02 0 03 and 0 04 second after the onset of QRS (7) magnitude of scalar components of eight instantaneous vectors dividing QRS in time into eight equal parts (8) spatial orientation of the polar vector of QRS (9) QRS duration (10) time interval between onset of QRS and peak of the R wave in lead X Measurements of the T wave was not included in order to avoid the lack of specificity of the repolarization process

Correlations between radiologic heart size and these measurements were evaluated by determining the incidence of cases with measurements outside normal ranges for each group of LVO The results were compared between the three groups of LVO with increasing heart size The measurements with the highest recognition rate for Group C and the lowest for Group A were considered to be optimal criteria to predict cardiac enlargement The normal range for each measurement was determined from records of 270 adult male patients without clinical evidence of past or present cardiovascular disease Since most of the measurements from normal records did not show normal distributions a 96 percentile range was used for setting normal limits This was accomplished by eliminating 2 per cent of normal samples on the high and low end of the distribution Such a normal range is comparable to a mean ± 2 standard deviations when a normal distribution is present

Results

The results of measurements of magnitude are shown in Table I The following items were selected for correlation (1) magnitude of the R wave in lead X (Rx) (2) magnitude of the R wave in lead Z (Rz) (3) the sum of these two magnitude values (Rx + Rz) (4) spatial magnitude of the maximal QRS vector (5) spatial magnitude of the time integral of QRS (SÂQRS) For each group of LVO percentages of the cases in which these measurements exceeded normal limits were determined The incidence of cases with high voltage for all of these items increased consistently with the increase in radiologic heart size The magnitude of SÂQI proved to be best for the recogniti

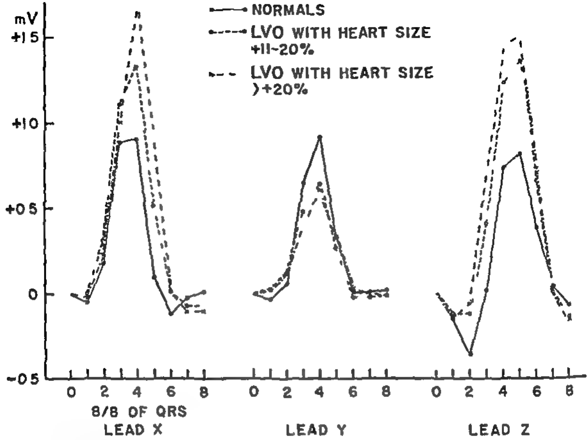

Fig. 1. Mean QRS configurations in three orthogonal leads for normal series and LVO groups. Positive polarity indicates leftward, inferior, and posterior directions for leads X, Y, and Z, respectively.

high voltage in the groups with radiologic evidence of cardiac enlargement. The sum of Rx and Rz, maximal QRS vector, Rz, and Rx were found to be less valuable in this order. In 9 cases of cardiac enlargement, high voltage was recognized only by increased magnitude of SAQRS. The percentages of cases in which the spatial magnitude of initial 0.02, 0.03, and 0.04 second vectors was outside normal ranges were generally low and did not show consistent trends with increase in heart size. These measurements, therefore, appear to be of little value.

A reduction in magnitude or absence of the initial QRS vector normally oriented to the right, superiorly, and anteriorly has been reported in some cases of LVO.[1, 3] As shown in Table II, there were no remarkable differences in the incidence of absence of Q waves in leads X and Y between the three groups of LVO. Furthermore, more than one third of the normal subjects also had no Q waves in these leads. Absence of Q waves in lead Z, on the other hand, was found exclusively in the groups with cardiac enlargement, although the percentages were small. The incidence of cases with a Q wave in lead Z but with an abnormally low Q/R ratio (< 0.10) was also higher for Groups C and B than for Group A: 29, 22, and 15 per cent, respectively. These findings of reduction or absence of the initial anteriorly oriented forces have generally been regarded as a diagnostic sign of anteroseptal infarction. It has to be realized, however, that the same findings can be present in a few advanced cases of uncomplicated LVO. Autopsy data were available in 2 of the 5 cases in which Q waves were absent in lead Z. In both cases, marked left ventricular hypertrophy was found without narrowing of coronary arteries, myocardial infarction, or significant fibrosis. Myers[16] reported similar findings.

Table I Percentage of cases with measurements of QRS magnitude exceeding normal limits for three groups of LVO

	Upper limit of normal (mV)	Group A— 34 cases (%)	Group B— 25 cases (%)	Group C— 41 cases (%)
Rx	1 95	29	24	44
Rz	1 90	12	24	49
Rx + Rz	3 50	2[illegible]	36	59
Maximal QRS vector	2 80	9	[illegible]4	51
SÂQRS	[illegible]0 0 μV sec	24	5[illegible]	68

Th[illegible] measureme[illegible] ar[illegible] sh[illegible] the l[illegible] Rx and Rz ind cate m[illegible] of R waves in th[illegible] scala[illegible] lead X and Z The maximal QRS vector a[illegible]d SÂQRS (time int[illegible]gral of QRS) ind cat[illegible] spat[illegible] m[illegible]gnitude

Table II Percentage of cases with absence of Q waves in three orthogonal leads

	Normal series— 270 cases (%)	Group A— 34 cases (%)	Group B— 25 cases (%)	Group C— 41 cases (%)
Lead X	39	38	5[illegible]	49
Lead Y	35	53	52	54
Lead Z	0	0	4	10

*Table III Percentage of cases with abnormal rightward displacement of point J**

	Group A— 34 cases (%)	Group B— 25 cases (%)	Group C— 41 cases (%)	Total— 100 cases (%)
Digitalized	25	50	67	58
Nondigitalized	30	41	65	42
Total	29	44	66	49

*See t[illegible] f[illegible] th[illegible] n[illegible]rm[illegible] l[illegible]m[illegible] [illegible] rightwa[illegible]d d[illegible]spl[illegible]cement of po[illegible]nt J

Table IV Percentage of cases with abnormal spatial orientation of various QRS parameters

	Group A— 34 cases (%)	Group B— 25 cases (%)	Group C— 41 cases (%)
QRS polar vector	[illegible]1	48	54
SÂQRS	6	12	7
Maximal QRS vector	12	[illegible]1	12
Initial 0 0[illegible] sec vector	21	28	27
Initial 0 03 sec vector	9	[illegible]8	41
Initial 0 04 sec vector	12	3[illegible]	44

Cabrera and Gaxiola[1] postulated that an augmentation of the Q loop oriented to the right and anteriorly was one of the characteristic findings in diastolic overload of the left ventricle whereas a reduction in or absence of the Q loop was a sign of systolic overload. In the present series, however, none of the 8 patients with isolated aortic insufficiency (diastolic overload) had a large Q wave which exceeded normal limits in lead X or Z. Instead, the Q wave was absent in lead X in all but 1 patient and was very small in lead Z in 3 patients with aortic insufficiency. On the contrary, abnormally large Q waves in lead X or Z were found in 4 patients with uncomplicated hypertension (systolic overload). Similar findings were reported by Sedziwy and Shillingford.[17]

Left axis deviation or superior shift of QRS has been known as another electrocardiographic sign of LVO.[14,18] In the present study the frequency of this sign was evaluated in terms of percentages of cases with an R/S ratio in lead Y smaller than the normal limit of 1.20. No remarkable differences were found between the three groups of LVO although the incidence increased slightly with an increase in heart size: 18, 24, and 27 per cent for Groups A, B, and C, respectively.

Fig. 1 illustrates the mean QRS configurations in the three orthogonal leads in 270 normal subjects and in the LVO patients with cardiac enlargement. These QRS configurations were obtained on the basis of mean values of the scalar components (X, Y, Z) of eight instantaneous vectors at points dividing QRS in time into eight equal parts. The purpose of this display is to demonstrate the average deviation of QRS from normal for both magnitude and orientation. The following tendencies of deviation from normal were observed for the mean QRS configurations of LVO patients (groups B and C): (1) reduced magnitude of early vectors normally oriented to the right, superiorly, and anteriorly; (2) increased magnitude of the middle vectors oriented to the left and posteriorly with a reduction of magnitude in the inferior direction; (3) increased displacement of the end of QRS or point J toward the right and anteriorly. This latter tendency was observed to some extent in the great majority of all LVO groups, 82, 88, and 91 per cent for Groups A, B, and C, respectively. The rightward displacement of point J appears to be of particular value in the recognition of cardiac enlargement. The incidence of cases with displacement of point J in lead X beyond the normal limit of 0.06 mV increased significantly with increase in heart size as shown in Table III. This trend was found similarly in both digitalized and nondigitalized patients. However, digitalized patients showed a higher incidence of this abnormality.

Correlations between radiologic heart size and spatial orientation of QRS parameters were evaluated for the QRS polar vector, SAQRS, the maximal QRS vector, and QRS instantaneous vectors at 0.02, 0.03, and 0.04 second after the onset of QRS. Table IV shows the incidence of cases in which the spatial orientation of these parameters was outside normal ranges. The spatial orientation was expressed by azimuth and elevation angles. The normal range was defined by encircling an area over the surface of a globe which included 96 per cent of 270 normal records. The percentages of cases with abnormal spatial orientation of the QRS polar vector and initial 0.03 and 0.04 second instantaneous vectors increased consistently with increase in radiologic heart size. No consistent trend was found for the spatial orientation of SAQRS, the maximal QRS vector, and the initial 0.02 second vector. The highest recognition rate of cardiac enlargement was found for spatial orientation of the QRS polar vector, which was abnormal in approximately one half of all LVO patients with cardiac enlargement. This vector defines the spatial QRS orientation as one single term. The usefulness of this parameter for the separation between normal and abnormal was reported previously.[19] Deviation of the direction of the polar vector with increase in heart size was found mainly in the inferior direction. As shown in Fig. 2 there was a close correlation between radiologic heart size and elevation angles of the polar vector direction when the latter deviated inferiorly beyond the normal limit of −18 degrees. Furthermore, the inferior deviation of this vector was

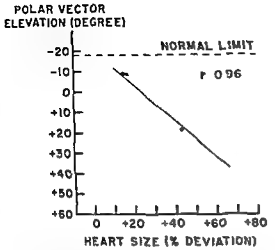

Fig 7 Correlation between elevation angles of QRS polar vectors and radiologic heart size Positive angles of the polar vector elevation indicate downward direction and negative angles indicate upward direction The normal range extend above the normal limit indicated by the dot-dash horizontal line r = correlation coefficient

found to accompany usually an alteration in the horizontal plane QRS loop configuration Ninety per cent of the cases with a narrow and/or figure of eight QRS loop in the horizontal plane projection had abnormal QRS polar vector directions whereas only 20 per cent of the cases with a wide open loop showed this abnormality These findings confirm previous observations in this laboratory [19, 9] The practical value of this parameter for prediction of cardiac enlargement is limited however because abnormal polar vector directions were associated with other QRS abnormalities in all but 1 case of LVO with cardiac enlargement

Table V shows the percentages of cases with prolonged QRS duration and prolonged time interval between onset of QRS and peak of the R wave in lead X (Rx peak time) The upper limit of normal was 0 112 second for QRS duration and 0 048 second for Rx peak time in the present normal series The latter measurement indicates prolonged duration of leftward directed forces to reach maximal magnitude The incidence of cases with prolonged Rx peak time increased consistently with increase in heart size Approximately one half of Group C was recognized by this measurement Prolonged QRS duration on the other hand was found only in small percentages of the LVO groups

A search for optimal single electrocardiographic criteria to indicate cardiac enlargement in patients with LVO was made and was extended to combinations of such criteria The following measurements were found to be best for this purpose (1) magnitude of S$\hat{A}$QRS greater than 66 0 μV sec (2) rightward displacement of point J greater than 0 05 mV (3) time interval between onset of QRS and peak of the R wave in lead X greater than 0 044 second Up to 4 per cent false positive cases were found in the normal series when each criterion was applied separately However the incidence of false positive cases could be reduced to zero when combinations of criteria 1 and 2 or 1 and 3 were applied The results for the three groups of LVO are shown in Table VI Seventy six per cent of Group C and 56 per cent of Group B were recognized by application of the described combinations of criteria Therefore the sensitivity of these combinations of criteria appears to be high

Since determinations of the time integral are very cumbersome for routine clinical application alternative procedures were tried to replace S$\hat{A}$QRS The sum of the magnitudes of the R waves in leads X and Z was found to be best as a replacement Through the use of a normal limit of 3 10 mV for Rx + Rz corresponding to the limit for S$\hat{A}$QRS false positive cases could also be eliminated completely The recognition rate for the three groups of LVO were then 18 per cent for Group A 48 per cent for Group B and 71 per cent for Group C

*Table V Percentage of cases in which QRS duration and Rx peak time exceed normal limits**

	Group A—34 cases (%)	Group B—25 cases (%)	Group C—41 cases (%)
QRS duration	9	8	15
Rx peak time	9	20	49

*Rx peak time indicates the time interval between onset of QRS and peak of the R wave in lead X [illegible] normal limit see text

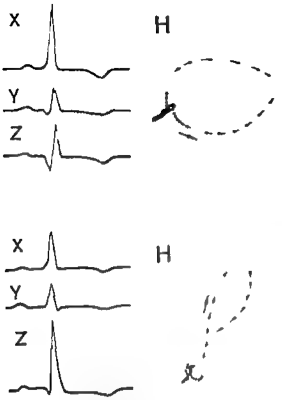

Fig. 3. Horizontal plane QRS loop configurations in LVO. The upper wide-open QRS loop was found mostly in cases without cardiac enlargement. The figure-of-eight configuration shown below was characteristic for cases with marked left ventricular enlargement. In some cases of LVO a transitional type of narrow loops without crossover was observed.

Thus, replacement of SÂQRS by this simpler measurement led only to a minimal decrease in the recognition rate for cardiac enlargement.

Besides these quantitative analyses of QRS parameters, configurations of QRS loops were also evaluated. The horizontal plane projection was found to be best for the recognition of cardiac enlargement in LVO. Eighty per cent of LVO patients with normal heart size (Group A) had a wide open QRS loop, whereas 60 per cent of those with cardiac enlargement (Groups B and C) had narrow and/or figure of eight configurations as illustrated in Fig. 3. The figure of eight configuration in particular was observed exclusively in Groups B and C. Horizontal plane QRS loop configurations therefore may give a clue for the prediction of cardiac enlargement in patients with LVO.

Discussion

In the interpretation of the results obtained in this study one has to keep in *mind the limitations of radiologic heart* size determinations as a measure of left ventricular overload. Concentric hypertrophy of the ventricular wall may not show an increase in radiologic heart size, whereas radiologic evidence of cardiac enlargement may be due to dilatation of the ventricle without hypertrophy. In most cases of long-standing LVO, however, *ventricular enlargement and hypertrophy* will both be present, depending upon the duration and severity of LVO. Furthermore, recent pathologic[1] and biplane angiocardiographic studies[2] indicated that there were no substantial differences in electrocardiographic manifestations between left ventricular hypertrophy and dilatation.

The data presented indicate that the magnitude of SÂQRS or Rx + Rz, rightward displacement of point J, and prolonged time interval between onset of

Table VI. Recognition rate of QRS criteria for three groups of LVO

QRS criteria		Criteria fulfilled		
		Group A—34 cases (%)	*Group B—25 cases (%)*	*Group C—41 cases (%)*
1. SÂQRS magnitude	> 66.0 µV sec	29	64	76
2. Rightward displacement of point J	> 0.05 mV	35	64	76
3. Prolonged Rx peak time	> 0.044 sec	18	44	71
Combinations of 1 + 2 or 1 + 3		18	56	76

QRS and peak of the R wave in lead X are by far the most useful QRS parameters for predicting cardiac enlargement in LVO

Increased magnitude or high voltage of QRS has been known as the most common electrocardiographic sign of LVO in orthogonal[14,18] as well as twelve lead electrocardiograms[4] In some studies however this sign was found to be absent in large percentages of autopsy proved cases of LVO[1,7] It has also been emphasized that this abnormality is most frequently responsible for false positive diagnosis of LVO[2,3]

The rightward displacement of point J is also known as a frequent finding in LVO[1,11,14] It has to be emphasized however that the value of this abnormality as a reliable diagnostic criterion for LVO is severely limited if used alone Many other conditions may lead to the same change

The time interval between the onset of QRS and the peak of the R wave in lead X corresponds to the left ventricular activation time of the older literature It has been known that prolongation of this time interval in left precordial leads is the most specific but infrequently encountered abnormality in LVO[2,3,6] Recently however Soloff and Lawrence[22] reported that this abnormality was found to be a highly sensitive and reliable sign of left ventricular enlargement when a more appropriate normal limit was used for this measurement

The application of combinations of two or more criteria for the diagnosis of LVO usually results in a sizable reduction in sensitivity[1] The combinations of selective criteria employed in this study however led to a complete elimination of false positive cases while maintaining a reasonably high degree of sensitivity Consequently the use of these criteria for the prediction of cardiac enlargement in LVO appears to be warranted

Various configurations of the horizontal plane QRS loop in patients with LVO have been described in other studies[12,15] Cabrera and Gaxiola[3] assumed the figure-of-eight QRS loop to be a sign of extreme overloading of the left ventricle complicated by chronic coronary insufficiency Wallace and associates[15] on the other hand ascribed this finding to incomplete left bundle branch block Our findings indicate that this abnormality is closely related to an advanced stage of LVO in which cardiac enlargement is always present

The described improvement in statistical correlations between the electrocardiogram and LVO may be due to two factors In the first place corrected orthogonal leads rather than conventional bipolar or unipolar leads were used Their relatively high degree of accuracy in lead direction and strength had been found previously to decrease normal ranges considerably[3] This may lead at the same time to a better separation between normal and abnormal The results of previous studies made in this laboratory strongly suggest such an improvement in diagnostic recognition[11] A second factor is the application of computer methods which allow testing of large numbers of diagnostic procedures in a very short time including statistical analyses In the present study emphasis was put on the search for simple electrocardiographic measurements which could be applied in routine practice Although some improvement in correlation appears to be possible by the use of more complex statistical procedures such improvements were found to be relatively insignificant with the present data

Summary

Correlations between radiologic heart size and electrocardiographic measurements of the QRS complex were performed in 100 patients with clinical evidence of left ventricular overload (LVO) Frank's corrected orthogonal lead system was used ECG analysis was performed by digital computation

Radiologic heart size correlated best with (1) spatial magnitude of the time integral of QRS (SAQRS) (2) the sum of R wave magnitudes in leads X and Z (3) rightward displacement of point J (4) time interval between the onset of QRS and the peak of the R wave in lead X Combinations of either one of the first two criteria with the third or fourth were found to be best for the recognition of cardiac enlargement in patients with left ventricular overload When the ... false positive cases was red...

zero the maximal recognition rate based solely on QRS criteria was 76 per cent.

A narrow and/or figure-of-eight QRS loop configuration in the horizontal plane projection was found frequently in cases with cardiac enlargement. This finding may serve as a clue for predicting left ventricular enlargement.

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Precordial movements in relation to age

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The purposes of this study were (1) to learn whether physiologic aging is associated with changes in precordial motions (2) to obtain base line data in normal persons over a wide range of age for future comparisons with data in patients suffering from cardiac disease and (3) to compare such qualitative alterations as may be found in healthy older persons with those reported by Skinner[1] in patients with congestive heart failure

Subjects and methods

Sixty five healthy ambulatory persons who ranged in age from 9 to 89 years were studied Measurements were also made on an additional 22 hospitalized patients with miscellaneous disorders Both groups were free of clinical and electrocardiographic evidence of cardiac disease and no subject had a diastolic blood pressure that exceeded 90 mm Hg

Electrocardiograms (Leads I and II) and carotid pulse tracings were recorded simultaneously with kinetocardiograms from multiple intercostal spaces in the V_1 to V_6 lines The technique used was that described previously All tracings were made during suspended breathing at the end of a normal expiration The major kinetocardiographic deflections which occurred during isovolemic contraction ejection and filling were studied These were measured as actual amplitude but in the several figures they are expressed as percentages of the total deflection which occurred during a single cardiac cycle Comparisons of relative amplitude tend to eliminate the effect of variations in the thickness of the chest wall

The various precordial deflections which are discussed in this report are illustrated in Fig 1 When because of involuntary breathing artifacts or unknown causes a given deflection exhibited unusual variability from cycle to cycle it was not recorded for that particular person

In the designation of the KCG traces the letter K indicates kinetocardiogram The first numeral in the subscript refers to the vertical V line and the second to the intercostal space Thus K_{13} indicates

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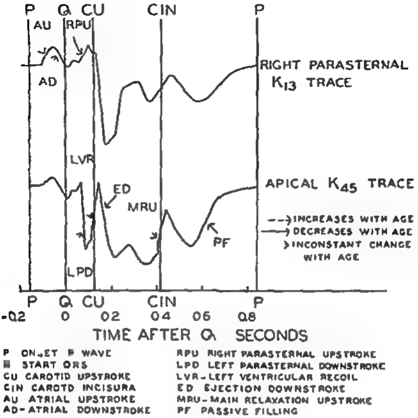


Fig. 1. Diagram of motion studied. The atrial motions (*AU* and *AD*) were measured in the upper right parasternal interspaces (K_{13} and K_{14}). The precise mechanism of this constant outward-inward sequence is unknown. The right parasternal upstroke (closure and bulge of tricuspid leaflets ?) was measured in the same region. The left parasternal downstroke and the reverse motion, the main relaxation upstroke (contraction and relaxation of the interventricular septum ?) were measured in the several lower left precordial regions. The ejection downstroke and passive filling upstrokes were studied in the same areas. The left ventricular recoil movement was measured only at the apex where it is largest.

the record from the right parasternal (V_1) line and the third intercostal space. Similarly, K_{45} refers to a trace from the fifth intercostal space in the mid-clavicular (V_4) line.

Results

Within a given age group, wide individual variations were noted. These are indicated in the several figures. Nevertheless, the measurements displayed certain trends with age.

I. Atrial motions. The data concerning the atrial motions (indicated as *AU* and *AD* in Fig. 1) are illustrated in Fig. 2. They displayed a wide scatter, but also apparently exhibited a trend. This is toward an increase in those movements which occur between P and Q with increasing age ($p < .05$).

COMMENT. The precise mechanism of the right parasternal motions related to atrial contraction is uncertain. Possibly the factors of recoil, change in volume, and alterations in position are all concerned.[4] In any case, it has been demonstrated by Skinner[1] that in the absence of atrial fibrillation the atrial motions are exaggerated in patients with congestive failure and improvement is accompanied by a decline in their amplitude.

We have not measured systematically the atrial motions in the apical region because a preceding study[3] indicated greater constancy of configuration of these movements when recorded in the right

parasternal line For this reason and also because of differences in recording technique our finding of a trend toward increasing parasternal atrial deflections with advancing age is not necessarily applicable to measurements made from apexcardiograms

II Main precordial motions during isovolemic contraction and relaxation These are illustrated in Fig 3

The right parasternal upstroke (indicated as *RPU* in Fig 1) which appears to be related to contraction of the right ventricle and which is probably due to closure and bulge of the tricuspid leaflets[4] exhibited a progressive decline with age The reverse was true of the left precordial inward motion (*LPD* Fig 1) which is attributed to activity of the left ventricle and probably to contraction of the interventricular septum[4]

The *largest motion during early relaxation* is the left parasternal outward deflection (*MRU* Fig 1) which occurs just before the carotid incisura and is attributed to relaxation of the interventricular septum[4] This motion increased with age (Fig 3)

III Motions related to ejection and filling The movements related to recoil and to the change in volume of ejection[4] (*LIR* and *FD* Fig 1) exhibited great variation in the older subjects These movements were large in some and very small in others Since no consistent change with age was

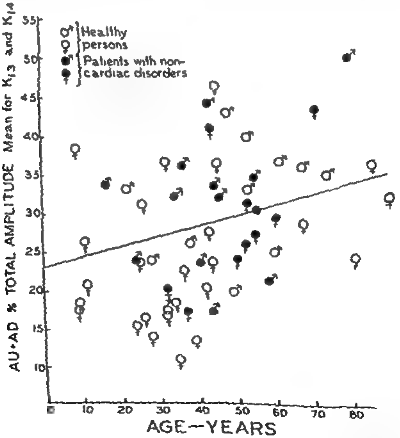
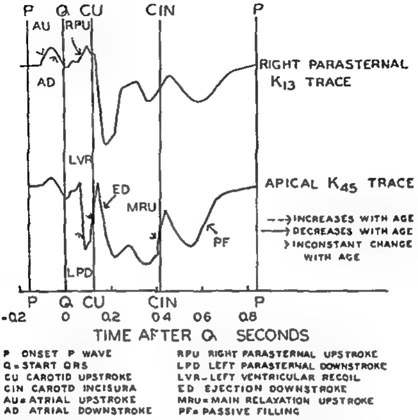


Fig 2 Relative size of atrial motion at different ages Traces from the right third and fourth parasternal lines were measured The amplitudes of both atrial motions (upstroke and downstroke) were added The points shown represent the mean values for the two interspaces The scatter is broad and the r value is only 085 The statistical probability that the upward trend with increasing age is due to chance is less than 5 per cent $y = 0\,135x + 22\,94$ The standard deviation is 19 77 Because of the wide scatter the lines indicating two standard [illegible] e not drawn



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IV Ratio of volume motion to atrial motion Several procedures tested for calculation of this ratio all yielded the same general result but the scatter was least with the method illustrated in Fig 5 A marked decline with advancing years was found in the quotient

$$\frac{\text{Passive filling upstroke}}{\text{Atrial upstroke} + \text{atrial downstroke}}$$

passive filling was measured at the three left precordial areas which displayed the largest total cycle deflection and the atrial motions were the average of those in the right parasternal line in the third and fourth intercostal spaces The decrease was apparent in the older premenopausal women as well as in the males and appeared to be logarithmic rather than linear (Fig 5)

Discussion

Before we evaluate these findings it may be well to consider whether such extracardiac factors as differences in the position of the heart or alterations in the thickness of the chest wall could be responsible for them

Changes in the location of the heart or in the compliance or other physical properties of the chest wall would be expected to alter the amplitude of all of the precordial motions throughout the cardiac cycle rather than changing a specific motion However those movements which have been cited as being respectively either larger or smaller in older subjects were changed in their relative amplitude as compared to the total deflection of the cardiac cycle It is improbable that changes in the physical characteristics of the chest wall could produce alterations in the relative size of one low frequency movement as compared to another Thus it is unlikely that extracardiac factors were responsible for the findings

During isovolemic contraction those motions attributed to right ventricular activity tend to be relatively large in children and young adults and to become progressively smaller in older subjects

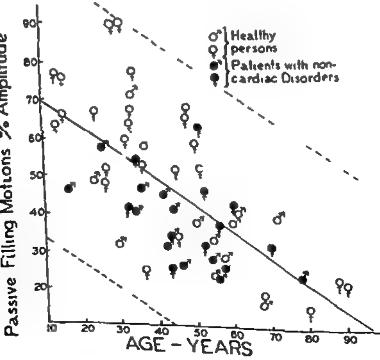

Fig 4 Passive filling motions in relation to age The points represent mean values for whichever three left precordial interspaces displayed the largest total excursion with the cardiac cycle The probability that the trend with age is due to cha[...]han 0 1 per cent (p < 001) $y = -0.6839x + 76.17$ r = 657 Sta[...]n = 18 04

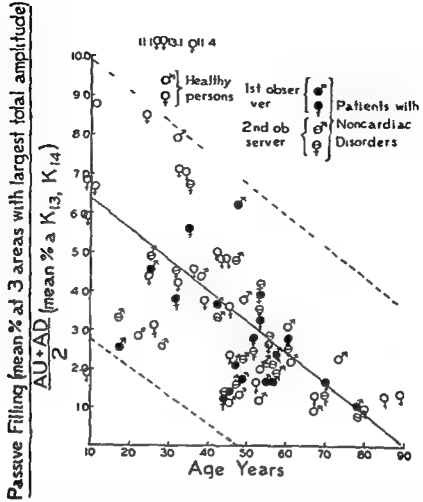

Fig. 5. Ratio of passive filling to atrial motions in relation to age. In order to avoid a large number of values below unity, the amplitude of the atrial motions ($AU + AD$) is divided by 2. The likelihood that the trend with age is due to chance is less than 0.1 per cent ($p < 0.001$). $r = -.554$, $y = -0.093x + 7.17$. Standard deviation = 1.754. The decline with age is logarithmic rather than linear. However, the regression equation and the correlation coefficient are calculated on a linear basis.

The reverse is true of the movements attributed to septal (or possibly left ventricular) activity. These observations are of interest in view of the well-known tendency toward right and left axis deviation in the electrocardiogram of young and old subjects, respectively. In the case of mechanical activity, as in that of electrical activity, the evidence of left ventricular predominance with increasing age need not mean an absolute increase in the work or thickness of that chamber. When deflections produced by one ventricle tend to be cancelled by opposite deflections produced by the other, a slight increase in the ratio of left ventricular work to right ventricular work would be expected to produce a relatively large change in the corresponding movements.

Since the cardiac output per minute of the two ventricles is the same, any significant difference in the ratio of right ventricular to left ventricular work should be reflected in the pressure loads on the two chambers. The published data on individuals who lacked evidence of structural cardiac disease[12-17] indicate that in early infancy there is an abrupt decline in the pulmonary pressure from the high fetal level. The right ventricular pressure

load then appears to remain relatively constant or to diminish slightly until age 40.[1, 15, 17] Whether there is any change after this age is uncertain in view of the paucity of observations on normal older persons.

Extensive data on systemic blood pressure have been published by Master and associates.[18] Their findings, based on many thousands of subjects, indicate a progressive rise with age; the average increment in diastolic pressure between the late teens and the early sixties is approximately 16 per cent. Thus the ratio of left ventricular work to right ventricular work tends to increase with age, and our observations suggest that this physiologic change is reflected in the corresponding precordial movements.

There is evidence for a decrease in stroke volume with age,[19] and it is probable that the progressive reduction in the outward motion of passive filling observed in the precordial traces is related to this. If all other factors remain constant, the atrial precordial movements will tend to parallel the vigor of atrial contraction, which will depend on the length of the fibers as contraction starts. In these thin-walled and readily distensible chambers, a slight rise in ventricular, and hence in atrial diastolic pressure, will tend to produce increased fiber length and more vigorous contraction. The trend toward augmented atrial parasternal motions in the older normal subjects suggests, therefore, that the ventricular diastolic pressures of older normal persons may be slightly higher than those of younger persons. Obviously, confirmation of these concepts by direct methods is needed by someone who is bold enough to measure intracardiac pressures or ventricular volumes in healthy older persons. It is likely that a large number of subjects would be required because the difference, if it exists, is probably small.

Even if it were assumed that because of the wide scatter of our data (Fig. 2) there is no change in atrial motions with advancing age, the observations herein cited would still point toward decline in myocardial reserve with advancing age. The ratio of passive filling motions to atrial motions is probably a crude index to the response/load quotient of the heart, because if other factors are constant, the numerator is related to stroke volume and the denominator to atrial stretch and hence to ventricular diastolic pressure (*see above*). Because there is striking correlation between increasing age and reduction in the relative size of the passive filling motion (Fig. 4), the ratio would be reduced even if atrial movements remained the same. To express the same concept in terms of more direct methods, one would say that, in view of the demonstrated[19] decline in stroke volume in older persons, there must be *a reduction either in ventricular diastolic stretch or in myocardial responsiveness*. The x-ray evidence that old hearts are not smaller but are of larger than average size[18, 20] suggests that the second alternative is correct. This interpretation is strengthened by the observation that persons with congestive failure display alterations in passive filling movements[1] and in atrial motions which, although of much greater magnitude, are in the same direction as those which occur as the result of the obscure mechanisms responsible for the aging process.

Summary

The precordial motions have been compared in various age groups. All subjects were free of clinical or electrocardiographic evidence of cardiac disease. Despite variations within a given age group, certain general trends were noted. Increasing age was accompanied by evidence of (1) a progressive decline in those motions ascribed to right ventricular activity, and a relative increase in those attributed to contraction of the left ventricle and/or interventricular septum; (2) certain changes which resemble in type, but not in extent, those seen in patients with congestive heart failure—(a) diminution of the outward movement due to passive filling, (b) a trend, despite wide variations within a given age group, toward increase in those right parasternal motions which are related to atrial contraction, and (c) a reduction in the ratio of filling motions to atrial motions. This indirect evidence of decline in output in relation to stretch points toward diminished efficiency in older hearts.

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Conditional reflex electrocardiogram of bulbocapnine

Conditioning of the T wave

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Conditional reflexes have been formed to many different functions beginning with Pavlov s work on the salivary gland in which he used an inborn stimulus (food) preceded by a bell [1] Then the sound of the bell acquires the property of the food in producing a conditional flow of saliva viz the salivary conditional reflex

The purpose of these experiments was to determine whether changes in the form of the ECG especially in the T wave can be conditioned on the pattern of what Pavlov did for the salivary gland Since there are so many aspects of cardiac activity it was necessary for the sake of precision to isolate one of these for study

By analogy with Pavlov s work on the salivary gland a substance (bulbocapnine†) was chosen which produces a change in the ECG and whose action on the heart is like food on the salivary gland of short duration The intravenous injection of bulbocapnine was preceded by a signal just as food is preceded by a signal to produce salivary conditional reflexes

Because of the complexities of including all the various cardiac reactions to the drug for the sake of making quantitative relationships without encumbering the procedure we selected for measurement chiefly the ECG heart rate respiration and gross movements Blood pressure was not included because it is essential to eliminate the presence of the experimenter (effect of person) during the measurements and a continuous automatic recording of blood pressure without the presence of the investigator was not possible

Materials and methods

In 3 mongrel dogs which ranged in weight between [illegible] and 13 kilograms a fine polyethylene tube (P E 100 I D 0 034 by 0 060 inches) was permanently implanted through the right external jugular vein into the right side of the heart This

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†Bulbocapnine HCl is an alkaloid substance derived from the bulb *Corydalis cava*.[2] It has been frequently employed to paralyze animals for short periods of time The drug 98 per cent pure was supplied by the New York Quinine and Chemical Works Inc.

chronic preparation permitted us to work with unanesthetized unrestrained dogs and to administer intravenous injections from a distance without the interference of the heart rate caused by the presence of the person in the same room with the dog[5]

A total of 169 experimental sessions was carried out for 19 months These dogs were trained to stand quietly on a platform inside a sound shielded room Observations of behavior were made through a one way window

In another dog (weight of 10 kilograms) assessment of the effects of the intracerebral injection of bulbocapnine was performed 2 days after the animal had been operated on under anesthesia for placement of an intraventricular polyethylene cannula in the region of the third ventricle The dog was sacrificed after these acute experiments in order to determine the area into which bulbocapnine was injected The total amount of bulbocapnine injected intracerebrally never exceeded 0 5 mg /kilogram

Standardized electrocardiograms three standard limb leads and three bipolar chest leads and a record of respiration using a transducer respirometer were taken concurrently from outside the room using an Offner type T machine A Fels cardiotachometer Model 21 A was also used to record instantaneous changes in heart rate

Controls before conditional reflex experiments For each dog the normal electrocardiogram in the sitting and in the standing positions was determined The effects of intravenous injections of normal saline tones and flashing lights on the ECG were determined *independently* in *order to* assess the effect of these stimuli on the ECG prior to conditioning

The effect of bulbocapnine HCl (unconditional reflex)* on the ECG was also determined during control experiments The drug was administered intravenously in doses which varied from 5 to 10 mg per kilogram diluted in a solution of 5 mg per cubic centimeter

Conditional reflex experiments Two signals were used as conditional stimuli a low intensity tone (500 c p s) as the excitatory conditional signal * and a flashing light (60 cycles per minute) as the inhibitory differential conditional signal † The duration of these conditional signals was always 15 seconds The flashing light was always presented first it was followed 2 minutes later by the tone The questioning reaction namely the orienting reflex[6,7] to the novelty of these stimuli was obliterated through repeated presentations prior to conditioning The orienting reflex has been described by Pavlov as the general response of the subjects to a new stimulus It is generally characterized by turning the head toward the stimulus

The flashing light was always presented without injection The tone was presented for 15 seconds reinforced with the intravenous injection of bulbocapnine during the last 5 seconds The presentation of the tone plus injection of the drug viz reinforcement corresponds to the reinforcement of the conditional stimulus by food or faradic shock used as unconditional stimuli in the classic Pavlovian paradigm One reinforcement was usually given each experimental day

The criteria of electrocardiographic conditioning were based on the appearance of T wave changes similar to those produced by bulbocapnine during the presentation of the tone without the injection of the drug provided that the auditory signal had been previously paired with the injection of the drug 20 or more times Because of *the fact that the effect of bulbocapnine on* behavior namely catalepsy can last a few hours it was decided to determine the establishment of the conditional reflex in *the electrocardiogram on experimental days* in which no drug had been injected in the early part of the experimental session

Results

Orienting reflexes The normal electrocardiogram of these dogs were similar to those reported by Lalich Cohen and Walker[8] and others[9,10] No evidence of

*Unconditional reflex is the *reaction which occurs in all* animals without training it is what physiologists ordinarily call *reflex*

*Any signal used as a conditional stimulus which is paired with an adequate unconditional stimulus such as bulbocapnine After many repetitions it produces changes similar to the unconditional stimulus

†When a signal somewhat similar to the conditional stimulus is repeated without reinforcement that is without being followed by the unconditional stimulus this unreinforced signal becomes inhibitory (differential)

abnormal electrocardiograms as described by Detweiler[11] was found prior to conditioning

The presentation of tones flashing lights, and injection of saline prior to the conditional reinforced trials never elicited any ECG change equivalent to that seen during the injection of bulbocapnine

Unconditional reflexes Figs 1 and 2 illustrate the electrocardiographic changes when bulbocapnine was injected into the right side of the heart and intracerebrally respectively The injection of bulbocapnine into the right side of the heart produced a marked tachycardia tachypnea and changes in the ECG mainly a marked alteration in the amplitude and direction of the T waves Frequently inverted T waves were reversed to an upright position and as a rule upright ones were increased in amplitude The changes in amplitude in the T wave were more prominent in the bipolar chest leads than in the standard limb leads The duration of the effect of bulbocapnine on the electrocardiogram was brief an average of 2 minutes and if it were *not* for the fact that continuous records were always taken most of these changes in the ECG would have been missed In some experiments the changes in the ECG lasted 5 minutes or more but seldom longer than 15 minutes In another series of experiments we found similar results by injecting the drug through the cephalic vein in the foreleg instead of into the external jugular vein

The intracerebral injection of bulbocapnine into the region of the floor of the third ventricle induced *neurogenic changes* in the electrocardiogram in the absence of gross convulsions These electrocardiographic changes are illustrated in Fig 2 The drug initially induced a marked tachycardia followed by bizarre changes in the ECG and bigeminy Tall T waves appeared initially 1 minute and 2 seconds after intracerebral injection and became very prominent after 3 minutes Behaviorally the animal appeared to be drowsy with occasional twitching of the face muscles After 30 minutes the electrocardiographic irregularities and tachycardia disappeared and the T wave was inverted in the standard limb leads and reduced in amplitude in the bipolar chest leads

Conditional reflexes After 20 or more reinforced conditional trials (which consisted always of a flashing light followed 2 minutes later by the reinforced low pitched tone) it was found that the presentation of tone without injection elicited changes in the ECG which were similar to those produced originally by the drug

Fig 3 illustrates conditional changes in the ECG to a nonreinforced low pitched tone The conditional reflex in the electrocardiogram occurred during the presentation of the tone and it disappeared abruptly after cessation of the auditory stimulus The conditional ECG changes consisted of tachycardia and tall T waves In one dog Vicky which showed clear-cut conditioning of the ECG we were able to duplicate these results after 2 weeks of rest from experimentation but the conditional ECG disappeared completely after 1 year The conditional ECG changes never occurred in response to the flashing light probably because the light came so long before the tone or because the light was a very weak delayed conditional stimulus Furthermore as shown by Pavlov visual stimuli in the dog are weaker than auditory stimuli

Fig 4 shows a conditional ECG in another animal after 50 reinforcements at which time a conditional tachycardia developed during a nonreinforced trial in which saline instead of bulbocapnine was injected during the tone Conditional tall T waves appeared after the abrupt cessation of the tachycardia These conditional changes were similar to those elicited previously by bulbocapnine but they were induced now by the presentation of the conditional stimulus (tone) plus injection of saline a combination that prior to conditioning did not elicit those changes Concurrent electroencephalographic recordings using scalp electrodes did not reveal any electroencephalographic abnormality

Injections of bulbocapnine were found to induce premature ventricular beats in one dog after 75 reinforcements (see Fig 5) This fact indicates that chronic reinforcements very likely recruit more elements in the neural pathway of the unconditional and conditional reflex because prior to 75 reinforcements neither the intravenous injection of the drug nor the con

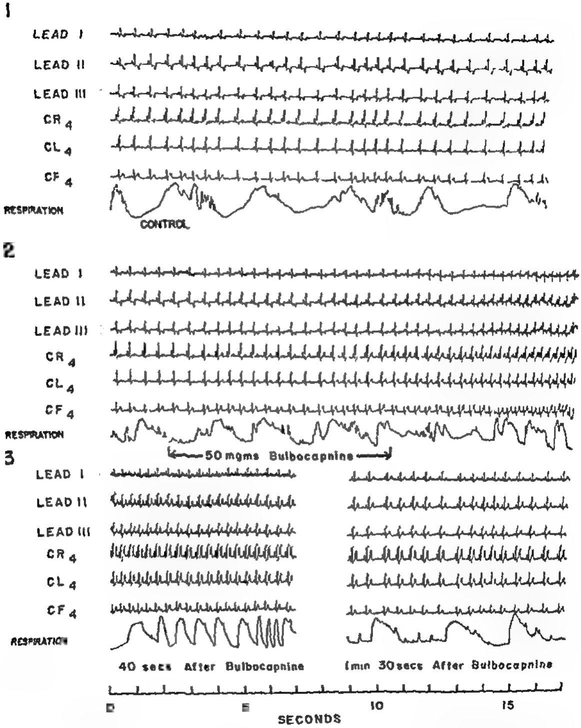

Fig *1* Electrocardiographic tracings showing the unconditional effects of bulbocapnine *1* Control electrocardiogram showing a pronounced sinus arrhythmia *2* Development of tachycardia 1 second after an intravenous injection of 50 mg of bulbocapnine directly into the right side of the heart *3* Unconditional increase in the amplitude of the T wave after injection of bulbocapnine

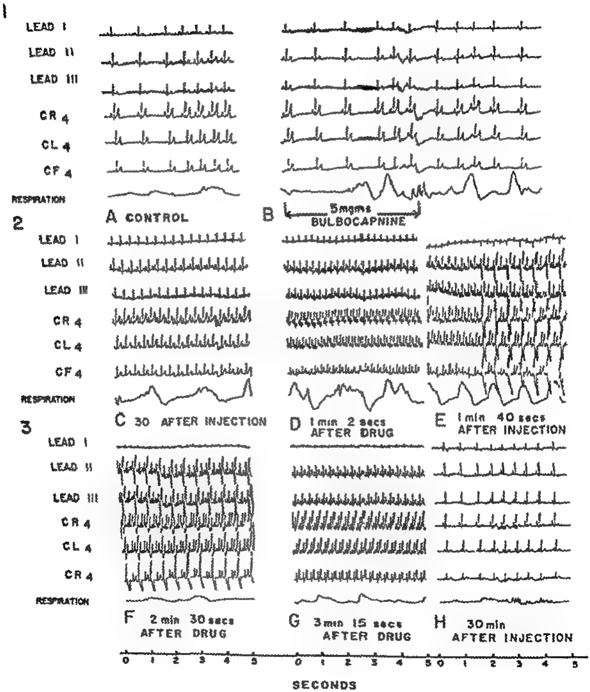

Fig 2 Unconditional electrocardiographic changes after intracerebral injection of bulbocapnine *1A* Control tracings *1B* Tracings during intracerebral injection of 5 mg of bulbocapnine *2C D E* Shows development of tachycardia changes in the amplitude of the T wave and bigemini *3F G H* Shows bigemini tall T wave changes and electrocardiographic tracing 30 minutes after injection

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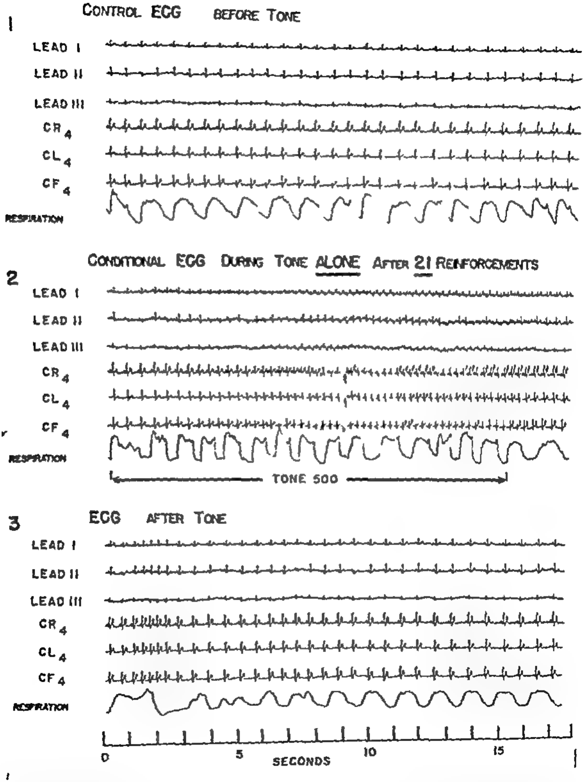

Fig 3 Conditional electrocardiographic changes due to tone alone after 21 reinforcements Tracings *1* *2* and *3* are continuous records *1* Control before tone *2* Conditional reflex electrocardiogram showing changes in the amplitude of the T wave and paroxysmal tachycardia during the presentation of the tone alone *3* Electrocardiogram after tone

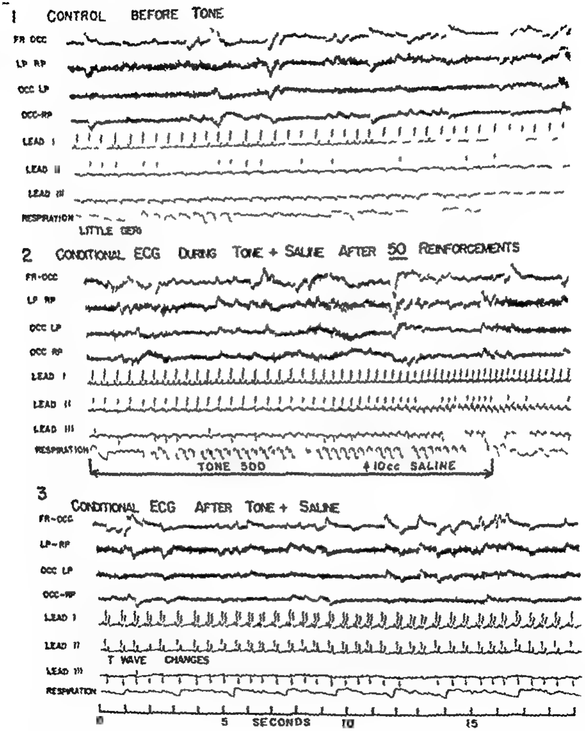

Fig 4 Conditional electrocardiographic changes during and after the presentation of a tone paired with an injection of saline after 50 reinforcements Concurrent electroencephalographic recordings were also taken *1* Control standard limb lead *2* Development of a paroxysmal tachycardia tachypnea and inversion of the T wave during the tone plus saline *3* Conditional T wave changes after tone plus saline Notice tall T waves in Lead I and II *FR OCC* Fronto-occipital *LP RP* Left and right parietal *OCC LP* Occipital left parietal *OCC RP* Occipital-right parietal

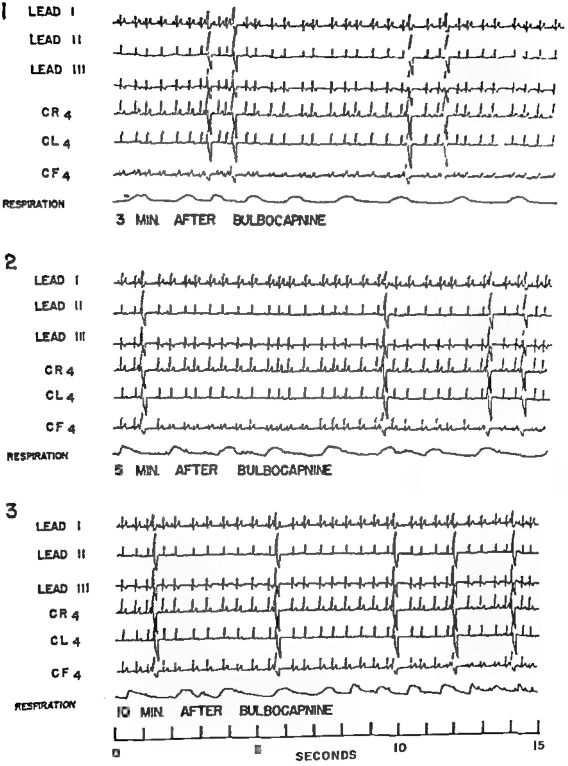

Fig 5 Development of unconditional extrasystoles after intravenous injection of bulbocapnine Tracings *1* *2*, and *3* show records taken at 3 5 and 10 minutes after injection

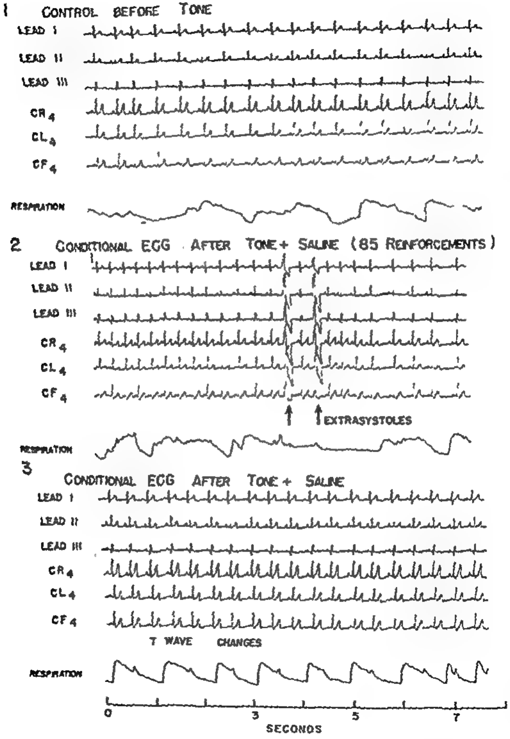

Fig 6 Conditional extrasystoles and T wave changes after 85 reinforcements *1* Control electrocardiogram before tone plus saline *2* Conditional extrasystoles immediately after the presentation of the tone plus saline *3* Conditional changes in the amplitude of the T wave after tone plus saline

stimuli plus injection of saline produced premature ventricular beats but *only* changes in the amplitude of the T wave Fig 6 *illustrates a conditional tachycardia* and induction of extrasystoles due to the tone plus saline after 85 reinforcements Conditional T wave changes were observed *after the tone plus saline*

The statistical analysis of the unconditional and conditional changes in the amplitude of the T wave comparing a control electrocardiographic tracing of the same duration as the tone using paired tests and Fisher statistical tables [1] showed that the T wave changes as well as the unconditional and conditional changes in heart rate were statistically significant (level of significance was set below 0 05)

Discussion

Previous work has shown that interoceptive conditional reflexes based on stimuli arising within the organism are as readily conditioned as are the somatic muscular responses Pavlov began his conditional reflex work with autonomic responses viz gastric and salivary secretions Bykov subsequently conditioned a variety of interoceptive responses—renal thermal metabolic hepatic splenic and endocrine

In the field of cardiovascular responses *Burch*[12] *has shown that the plethysmographic* reflexes in the human being can be *conditioned as a component of the orienting* reflex

Bykov has conditioned vascular constriction and dilatation as well as cardiac reflexes He claimed to have conditioned ECG changes to a variety of substances—morphine nitroglycerin adrenaline strophanthin and acetylcholine [14] However from an examination of his records available to us it appears that of the above mentioned substances there is only unequivocal ECG conditioning to nitroglycerin and possibly strophanthin

From our past work we do not believe that the effect of any agent which is produced by peripheral action solely without *involvement* of the central nervous system can be conditioned Using atropine and acetylcholine[15,16] to produce tachycardia histamine for gastric secretions [17] pilocarpine for salivary [18] or for prostatic secretions [19] and adrenaline for hyperglycemia [20] we have been unable to obtain conditional reflexes When an agent produces some effects through the central nervous system and others via the periphery the central nervous system effects can be conditioned whereas the peripheral effects cannot This is what we call fractional conditioning [1]

Our experiments differ from those of Bykov s in that we scrupulously separated the person from the dog during the injection of the drug (injection from a distance) because the person himself can have a more marked effect than even atropine [20] especially on heart rate

From our work it appears that the criterion for ECG conditioning is the involvement of the central nervous system in evoking the particular reaction viz *the mechanisms by which the response is* produced rather than the nature of the response itself—any response mediated by the central nervous system is conditionable

Our experience with bulbocapnine shows that not only can the motor phenomena *namely the catalepsy be conditioned* as previously reported [3,4] but that the very marked ECG pattern of bulbocapnine is almost exactly duplicated by the conditional stimulus either by saline or by an auditory stimulus preceding the injection *The resemblance of the ECG pattern of* bulbocapnine to that elicited by the con*ditional stimulus leaves no room for* doubting the presence of the conditional reflex in the ECG pattern

The durations of the conditional ECG and the unconditional reflexes to bulbocapnine itself are markedly different the conditional reflex is shorter lasting not much longer than the conditional stimulus itself whereas the effect of bulbocapnine on the ECG continues for 2 minutes or more

Although we have found that the conditional tachycardia as a component of food or pain reflexes is very resistant to extinction [5] the conditional ECG pattern is rather transient weak and labile disappearing after a few nonreinforced repetitions of the conditional stimulus i e without the injection of bulbocapnine

The explanation of why the ECG pattern of bulbocapnine can be conditioned

whereas the tachycardia due to acetyl choline atropine etc cannot probably rests upon the fact that the effect of bulbocapnine on the ECG is mediated through the central nervous system We have obtained some evidence for this by producing the same ECG pattern after intracerebral injection of bulbocapnine The possibility of a transfer of bulbocapnine through the circulation to the peripheral structures in the heart after intracerebral injection is not ruled out but only 0 5 mg per kilogram (total of 5 mg) was injected and usually at least 40 mg or more depending on the weight of the animal is required to produce electrocardiographic changes when the drug is injected into the circulation

The experiments support the clinical impressions that in the normal organism the heart is strongly influenced by the higher nervous system including nervous structures rostral to the midbrain and medulla More impressive is the fact that the repolarization processes of the ventricles represented by the T wave are under the direct influence of the central nervous system and that psychophysiologic experiences can alter these same processes

Summary

We studied conditioning to a drug bulbocapnine which produces marked motor effects (catalepsy) as well as profound changes in the electrocardiogram The latter consist mainly in changes in the amplitude of the T wave in standard limb leads and greatly exaggerated T waves which are equal in height to the R wave in *bipolar precordial leads*

Separating the dog from the interference of the presence of a person and using injection of the drug from outside a sound shielded room we were able to demonstrate a conditional electrocardiographic change after 20 repetitions The conditional reflex was formed to the *signals* of the intravenous injection (without the presence of the person) namely to the injection of saline or to auditory signals

The effects of bulbocapnine (catalepsy and ECG pattern) are mediated through the central nervous system in contrast to certain effects of atropine and of choline on cardiac functions The fact that cardiac changes due to bulbocapnine (centrally acting) are conditionable whereas those due to atropine and other peripherally acting substances are not conditionable is further evidence that the criterion for conditioning is not the type of response but *whether it is mediated peripherally or centrally*

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Cardiovascular reactions in asphyxia and the postasphyxial state

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In a preceding paper[14] it was shown that stimulation of and lesions in the hypothalamus as well as reflexly induced changes in the state of the hypothalamus lead to characteristic changes in cardiovascular reactions States of increased sympathetic discharges were accompanied by enhanced sympathetic and decreased parasympathetic reactivity whereas the reverse changes occurred in states of increased parasympathetic discharges

It is the purpose of this paper to discuss the validity of these findings for the state of asphyxia chosen because of its profound yet reversible action on the autonomic system[5,10,15] and its relation to cardiovascular diseases [2]

Methods

The investigations reviewed in this paper† were performed on cats prepared under light barbiturate and local anesthesia which was later supplemented by Intocostrin Artificial respiration was used routinely The blood pressure (femoral artery) and contractions of the nictitating membranes were recorded by means of Statham pressure transducers and Statham dynamometers with a Brush amplifier and oscillograph The pulse rate was recorded with an ordinate writer an increase in the vertical stroke indicated a decrease in the pulse frequency The hypothalamus was stimulated by means of a square wave generator through Hess electrodes Asphyxia was produced by clamping the tubes to the tracheal cannula Drugs were injected intravenously Denervation of the sino aortic area followed standard surgical procedures

I Asphyxia and sympathetic reactivity

Fig 1 may serve to distinguish between several phases of asphyxia during which the sympathetic and parasympathetic responsiveness undergoes characteristic changes It is seen that during the first two thirds of the period of asphyxia (early phase) the blood pressure rises whereas in the last third (late phase) the pressure falls progressively and reaches eventually shock levels During the early phase sympathetic signs (rise in blood pressure and heart rate dilation of the pupils and contraction of the nictitating membranes) occur during the late phase the blood pressure falls and the pulse rate is slowed There is however no strict parallelism between the last two phenomena As illustrated in the experiment of Fig 1 the maximal pulse rate may be attained in the late phase when the blood pressure has fallen below the initial value

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Fig 1 Phases of sympathetic and parasympathetic dominance during and after asphyxia (85 seconds indicated by the long horizontal bar) *Early asphyxia* Rise in blood pressure and acceleration of the heart rate *Late asphyxia* Fall in blood pressure and heart rate *Early postasphyxial state* Rapid brief rise in blood pressure and heart rate *Late postasphyxial state* Prolonged slowing of heart rate while a high level of blood pressure is maintained Increase in ordinate of PR indicates a fall in pulse rate [6]

After the readmission of air or oxygen there is a brief phase ("early postasphyxial phase") during which the heart rate and blood pressure rise rapidly Depending on the degree of anesthesia the duration of the preceding asphyxia and similar factors a contraction of the normal nictitating membrane and often also of the denervated nictitating membrane (*n n m* and *d n m* respectively) occurs at this time This phase is followed by a prolonged period during which the blood pressure rises gradually and is maintained at an elevated level for one or more minutes During this late postasphyxial phase the pulse pressure is greatly increased and the pulse rate is slowed

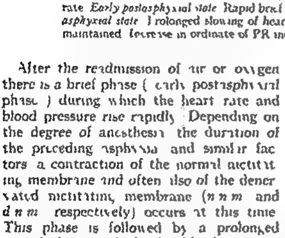

Fig 2 The effect of acetylcholine (injection indicated by the arrow) during asphyxia Acetylcholine elicits stronger sympathetic reflex effects during asphyxia (*C*) than under control conditions (*A*) Note the greater acceleration of the pulse rate and the quicker return of the blood pressure from the hypotensive phase *A* Acetylcholine intravenously 7.5 gammas *B* Sixty seconds of asphyxia. *C* Sixty seconds of asphyxia with 7.5 gammas of acetylcholine intravenously at 30 seconds of asphyxia [6]

Numerous experiments showed that the sympathetic reactivity is greatly increased during the early phase of asphyxia If the sympathetic division of the hypothalamus is stimulated the rise in blood pressure and heart rate and the contraction of the nictitating membranes are much greater than during the preasphyxial control period Similar results are obtained when the test stimulus is applied to the vasomotor center in the medulla oblongata Particularly striking results are seen when a test stimulus of near threshold intensity is chosen and also when the stimulus is applied early in asphyxia before signs of sympathetic excitation are manifest Under these conditions it is noted that the increase in sympathetic reactivity in the early phase of asphyxia is much greater than the algebraic sum of the effects produced by asphyxia and the test stimulus when applied separately

Similarly it is found that hypotensive drugs elicit stronger sympathetic reactions during asphyxia than under control conditions Fig 2 illustrates the action of acetylcholine and asphyxia administered separately (*A B*) and in combination (*C*) The greater sympathetic effect produced by acetylcholine during asphyxia is evident from the fact that the recovery of the blood pressure from the hypotensive action of the drug is more rapid during asphyxia than in the control test (*A*)* Moreover the heart rate increases more in response to acetylcholine during asphyxia than in the control period (*A*) and the maximal rise in blood pressure during asphyxia is greater when acetylcholine

*The acetylcholine-induced hypotensive area was found to be 30 to 80 per cent smaller in asphyxia than in the control test

had been administered (*C*) than without it (*B*). This rise in blood pressure is in the former case (*C*) associated with an increase in pulse pressure which is absent in test *A* and slight in *B* of Fig. 2. Similar results are obtained with Mecholyl and histamine. As pointed out previously,[5,7,8] the mechanism involved in these experiments is the release of the sympathetic centers from the restraining action of the baroreceptors of the sino-aortic area.

It seems to follow that the sympathetic action produced by stimulation of medullary or hypothalamic centers or resulting from their release from the tonic activity of the baroreceptors is greatly increased during the early phase of asphyxia.

It was mentioned earlier that the late asphyxial phase is characterized by a fall in blood pressure associated first with an increase and later with a decrease in heart rate. After the vagi had been cut the acceleration of the pulse rate persisted throughout this phase. This indicates that sympathetic *and* parasympathetic discharges are increased in late asphyxia with the latter predominating in the cardiovascular action. Nevertheless the increased reactivity of the sympathetic system persists under these conditions as tests with direct hypothalamic stimulation or with hypotensive drugs indicate.

Fig. 3 shows an experiment in which asphyxia administered for 90 seconds led first to a rise and then to an abrupt fall in the blood pressure. A hypothalamic near threshold stimulus which under control conditions evoked only a small contraction of the normal nictitating membrane (see the effect of the first stimulus applied in *B* and also in part *C* of Fig. 3) elicited during the late phase of asphyxia a strong sympathetic reaction on the normal nictitating membrane and in addition a moderate contraction of the denervated nictitating membrane, the latter signifying an adrenomedullary discharge. Two phenomena are of interest in this record. (1) Although during this phase of asphyxia the sympathetic effects on blood pressure or heart rate are not apparent,* the reactivity of the sympathetic nervous system is increased as indicated by the responses of the normal and denervated nictitating membranes.

*This reason seems to be the dominance of vagus in this phase (and possibly also some damage to the heart), yet peripheral sympathetic discharges are increased.[18]

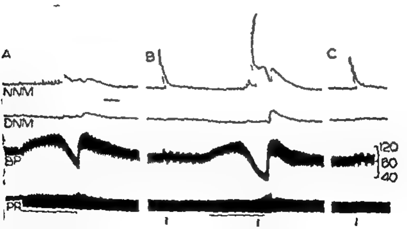

Fig. 3. Hypothalamic stimulation during prolonged asphyxia. *A*, Ninety seconds of asphyxia. *B*, Hypothalamic stimulation indicated by a vertical line (1.5 V, 100/sec, 1.6 ms, for 15 seconds) before asphyxia and 80 seconds after the onset of 90 seconds of asphyxia. *C*, Hypothalamic stimulation as in *B*. Note that the hypothalamic stimulus applied during the late phase of asphyxia elicits a greatly increased contraction of the normal nictitating membrane (*NNM*) and a contraction of the denervated nictitating membrane (*DNM*) (signifying adrenomedullary secretion) in *B*, although neither asphyxia as such (*A*) nor the hypothalamic stimulus by itself (*C*) evokes the latter reaction.*

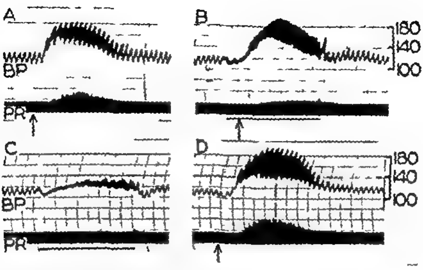

Fig. 4. The noradrenaline-induced pulse slowing during asphyxia. *A*, Noradrenaline (*arrow*) 0.0033 mg./Kg. intravenously. *B*, Noradrenaline (as in *A*) injected 7 seconds after the onset of a 50 second period of asphyxia. *C*, Fifty seconds of asphyxia. *D*, Noradrenaline 0.005 mg./Kg. intravenously.

(2) This intensification of the sympathetic responsiveness to a hypothalamic stimulus leads to effects which are far greater than can be accounted for by an algebraic summation.

It should be mentioned that this conversion of a neurogenic sympathetic effect into a neurogenic *and* hormonal action which involves the adrenal medulla is likewise observed in early asphyxia in response to direct or reflex stimulation of the hypothalamus. Similar effects are seen under control conditions when the intensity of the hypothalamic stimulation is increased.[3]

II. Asphyxia and parasympathetic reactivity

That the reactivity of the parasympathetic system is lessened during the early phase of asphyxia while overt signs of increased sympathetic discharges prevail was shown in several groups of experiments. The first involves baroreceptor reflexes resulting from the injection of noradrenaline. Thus the noradrenaline-induced slowing of the heart rate is less during asphyxia (Fig. 4 *B*) than in the control test (*A*). This occurs in spite of the fact that the rise in blood pressure is greater in *B* than in *A*, a condition which in the absence of asphyxia would produce an even greater slowing of the heart than was recorded in *A*. To obtain a measure of the influence of asphyxia on parasympathetic reactivity, a slightly larger dose of noradrenaline was injected in *D*, the effect of which matches approximately the blood pressure curve recorded in *B*. The difference between reflex slowing of the heart rate shown in *D* and *B* indicates the asphyxia-induced diminution in parasympathetic reactivity.

The baroreceptor reflexes evoked by the hypothalamically induced rise in blood pressure are commonly suppressed in the normal animal since the pressor effect is associated with a rise in the heart rate. If, however, the sympathetic responsiveness has decreased as the result of frequent hypothalamic stimulations, the baroreceptor reflexes reappear so that a hypothalamically induced rise in pressure is accompanied by a moderate reduction in heart rate. Under these conditions it can be shown that the slowing of the heart rate due to a hypothalamic stimulus is less in asphyxia (Fig. 5 *B*) than during inhalation of air (Fig. 5 *A*). Fig. 5 *C* shows the reversibility of this action.*

In a second group of experiments a reduction in the responsiveness of the parasympathetic system during the early phase

*When asphyxia was applied by itself, no significant changes in heart rate were observed during and after asphyxia (duration 35 seconds).

of asphyxia was also seen when the central end of the sciatic nerve was stimulated with square wave currents of low frequency (10 per second or less) The fall in blood pressure in response to this stimulus was less in asphyxia than during inhalation of air

In a final group the slowing of the heart rate which follows abruptly the stimulation of the hypothalamus[8] was utilized for the study of parasympathetic reactivity in early asphyxia Fig 6 (*middle section*) shows that this parasympathetic rebound is greatly reduced in asphyxia In some experiments the rebound appears in the pulse *and* blood pressure records Whereas blood pressure and heart rate rise during stimulation the blood pressure falls below the control level in the poststimulation period while the heart rate slows abruptly Both rebound phenomena were found to be reduced greatly and reversibly during the early phase of asphyxia

A fundamentally different behavior of parasympathetic reactions is observed in the *late* phase of asphyxia during which the blood pressure and heart rate decrease If during this phase a hypothalamic stimulus of low frequency (8 to 10 per second) is applied it evokes a much greater fall in blood pressure and heart rate than that which occurs under control conditions

It is concluded from these experiments that asphyxia reduces parasympathetic excitability during the early phase when the sympathetic system is dominant and increases parasympathetic responsiveness in the late phase of asphyxia when the parasympathetic system is dominant

III Autonomic reactivity in postasphyxial state

The *early* postasphyxial phase (see Section I) shows the characteristics of increased sympathetic or sympathetico adrenal discharges Stimulation of the sympathetic division of the hypothalamus was found to be more effective in this phase than under control conditions as indicated by a greater rise in blood pressure and increased contraction of the nictitating membranes This phase shares therefore the characteristics of the early asphyxial period

The late postasphyxial phase characterized by a gradual rise in blood pressure and maintenance of this elevated pressure for minutes while the heart rate is reduced showed a lessened responsiveness of the sympathetic system The pressor effect and the action on the nictitating membrane elicited by stimulation of the posterior hypothalamus under control conditions is much greater than that observed when this stimulus is applied during the late postasphyxial phase Not infrequently it is seen that after stimulation the pressor effect is not merely diminished but is converted into a depressor effect accompanied by cardiac slowing Moreover sciatic stimulation of low frequency causes a greater fall in blood pressure and heart rate during this postasphyxial phase than that which is seen under control conditions

Discussion

By adoption of the terminology used in preceding investigations[3] the early asphyxial and postasphyxial phases which show overt signs of increased sympathetic activity may be described as states of sympathetic tuning whereas the late asphyxial and postasphyxial phases which show overt signs of increased parasympa

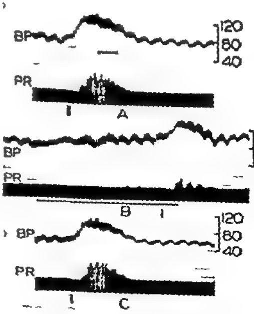

Fig 5 A and C Hypothalamic stimulation (... 100 pps 1 6 ms for 4 seconds) B Asphyxia (... xial ba) with hypothalamic stimulation ... d after beginning of asphyxia (unpubl

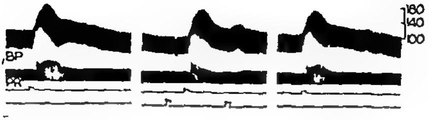

Fig 6 *Left and right* Stimulation of the left posterior hypothalamus (1 5 V 207 pps 0 8 ms for 3 seconds) *Middle* Forty five seconds of asphyxia indicated by the lower signal magnet with hypothalamic stimulation as in 1 15 second after the onset of asphyxia (unpublished)

thetic activity are looked upon as states of parasympathetic tuning The chief results obtained in this investigation may then be expressed as follows

1 *Asphyxial and postasphyxial states* of sympathetic tuning are characterized by an increased responsiveness of the sympathetic system to stimuli acting on the sympathetic centers of the hypothalamus or medulla oblongata directly or via reflexes

2 Asphyxial and postasphyxial states of parasympathetic tuning show an increase in parasympathetic reactivity to reflex or direct stimulation of parasympathetic centers

3 Reciprocal relations are demonstrable in the early asphyxial and the late postasphyxial states In the former the increased sympathetic responsiveness is associated with a lessened parasympathetic responsiveness whereas in the latter the reverse relation obtains

4 A reversal in response to sympathetically acting stimuli may occur in the late postasphyxial state a stimulus which elicits a rise in blood pressure and heart rate under control conditions may in this phase produce a fall in blood pressure and pulse rate

These results are similar to those described in earlier investigations[9,11] in which states of sympathetic and parasympathetic tuning were produced by direct or reflex stimulation of the hypothalamus or the medulla oblongata A rise in blood pressure induced by hypothalamic stimulation (sympathetic tuning) led to an increased sympathetic reactivity whereas a similar rise produced by the injection of noradrenaline led to an increased parasympathetic (and a decreased sympathetic) reactivity Similarly it was seen in the present work that the rise in blood pressure produced by the early phase of asphyxia showed the characteristics of sympathetic tuning whereas an increase in blood pressure of similar magnitude occurring in the late postasphyxial phase disclosed the signs of parasympathetic tuning Consequently *it is not the level of blood pressure* which determines vasomotor and cardiac responsiveness but the nature of the antecedent stimuli and their specific action on the centers of the autonomic nervous system

The record of the rise in blood pressure associated with a slowing of the heart rate which follows the injection of noradrenaline is similar in appearance to the records of blood pressure and heart rate seen in the late postasphyxial phase The physiologic characteristics of these states are likewise similar a state of parasympathetic tuning prevails The behavior of the normal and denervated nictitating membranes seems to indicate that the *late* postasphyxial phase is associated with or preceded by adrenomedullary secretion[16] Apparently injection as well as secretion of adrenomedullary humors leads to a state of parasympathetic tuning

Numerous experiments showed that states of sympathetic or parasympathetic tuning regardless of whether they were induced by direct or reflex activation of autonomic centers or by a change in the internal environment such as asphyxia illustrate the validity of the law of reciprocal relations In states of sympathetic tuning the parasympathetic reactivity is lessened and vice versa The *late* asphyxial

phase, however, shows special characteristics which deviate from this scheme. As pointed out earlier, sympathetic as well as parasympathetic discharges are increased under these conditions. Correspondingly, it is found that the sympathetic *and* the parasympathetic reactivity is augmented.*

Although asphyxia increases the activity of the sino-aortic chemoreceptors and contributes thereby to the excitation of sympathetic centers in the medulla oblongata and hypothalamus, these central autonomic structures still respond to asphyxia (but not to anoxia) with a rise in in blood pressure after sino-aortic denervation.[14,15] Moreover, the increased responsiveness of the sympathetic division of the hypothalamus to direct stimulation persists after the elimination of the sino-aortic receptors, but seems to be somewhat lessened.[6,7] This suggests that the increased sympathetic responsiveness in asphyxia is due to its action on the chemoreceptor *and* autonomic centers.

Asphyxia served in this study as an example to illustrate the important fact that changes in the internal milieu may alter the reactivity of the autonomic system. That this work is of importance for the clinic is suggested by the findings of increased retention of carbon dioxide in and deficient oxygenation of the arterial blood in *cardiovascular* and respiratory diseases.† It is not unlikely that even mild changes in metabolism may induce similar changes in autonomic reactivity. Although not so completely investigated as the case of asphyxia, it is known that an increase in the concentration of carbon dioxide in the inhaled air increases sympathetic discharges and sympathetic reactivity at the medullary and hypothalamic level.[2,4] It was further shown that lesions in the posterior hypothalamus greatly reduce the peripheral *autonomic*[3] as well as the cerebral[17] manifestations of hypercapnia and that in this state the parasympathetically acting stimuli (rise in sino-aortic pressure due to the injection of noradrenaline) are less effective than under control conditions.[1] Apparently the sympathetic reactivity is increased and parasympathetic responsiveness is lessened during hypercapnia. Since the oxygen and carbon-dioxide tension and also the concentration of glucose in the blood influence the degree of activity of the autonomic nervous system, it is suggested that, in clinical conditions in which such changes in the internal milieu occur, cardiovascular reactions may be modified according to the rules established in this investigation.

Summary

The reactivity of the autonomic nervous system was investigated in anesthetized cats during and after a period of asphyxia. The findings made were these: (1) In early asphyxia and immediately after the readmission of air or oxygen after a period of 60 to 90 seconds of asphyxia there is a phase of rising blood pressure and heart rate which indicates increased sympathetic discharges. During this phase of sympathetic "tuning" the sympathetic reactivity is increased. (2) In late asphyxia and also in the late postasphyxial phase there is a period in which parasympathetic discharges are dominant. This is seen in the fall of blood pressure and heart rate during late asphyxia, whereas a slowing of the heart rate in the late postasphyxial state occurs while the blood pressure remains elevated as though a marked adrenomedullary secretion had taken place. During this state of parasympathetic "tuning" the parasympathetic reactivity is increased.

The validity and limits of the law of reciprocal relations in asphyxial and postasphyxial states are discussed.

The laws of "tuning" of the autonomic nervous system established earlier in experiments involving alterations of autonomic functions as the result of direct or reflexly induced excitation of autonomic centers are confirmed in states in which the internal environment is changed. It is stressed that not the level of blood pressure but the nature of the autonomic discharges which produce this level d-

*The law of reciprocal relations does not seem to hold under the influence of strong stimuli which activate both branches of the autonomic system. This was shown earlier by studies on blood sugar. They indicated that a variety of conditions elicited discharges in the sympathetico-adrenal as well as in the vago-insulin system.[5] It may be added that changes in internal environment such as those produced by hypoglycemia are known to lead to increased sympathetic and vagal discharges.[5]

†See Reference 2 for the literature.

sympathetic and parasympathetic reactivity quantitatively and qualitatively A rise in blood pressure which results from asphyxia in its early phase is accompanied by an increase in sympathetic and a decrease in parasympathetic reactions but a similar rise in blood pressure which occurs in the late postasphyxial phase is associated with the reverse changes in autonomic excitability

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Activation of the free wall of the right ventricle in experimental right ventricular hypertrophy with and without right bundle branch block

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There is a large volume of clinical electrocardiographic literature concerning the varied QRS patterns associated with right ventricular hypertrophy, yet the details of right ventricular activation in the presence of hypertrophy and block remain obscure. Although there are a few reports in which precordial, epicardial, and intracavitary potentials have been analyzed in patients with Fallot's tetralogy,[1] pulmonary stenosis with intact ventricular septum,[2,4] and mitral stenosis, data from direct experimentation in the laboratory are not available. Unfortunately, it is not possible to deduce the essential details of ventricular depolarization in either the experimental animal or man from a study of the variations in potentials recorded only at the precordium, epicardium, and/or ventricular cavity.[5] Therefore, the present experiments were designed to compare the details of the accession process in the hypertrophied right ventricle in the dog, using intramural electrodes, with observations of normal right ventricular activation reported previously.[6] The data obtained are believed to be relevant to a basic understanding of the electrocardiographic changes which occur in man when right ventricular hypertrophy with or without right bundle branch block is present.

Methods

Production of right ventricular hypertrophy. Forty-eight dogs 4 to 8 weeks old were subjected to left lateral thoracotomy under thiopental sodium anesthesia. The pericardium was opened and the main pulmonary artery was dissected free from the aorta. A broad cotton ligature was placed at the immediate supravalvular level to prevent expansion of the vessel with

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growth this led to the development of pulmonary artery stenosis and subsequently to right ventricular hypertrophy Of the 48 animals 12 survived with satisfactory evidence of right ventricular hypertrophy the average thickness of the free wall of the right ventricle was 11 6 mm (normal 3 to 4 mm) Four animals developed ventricular fibrillation at the time that attempts were being made to sever the right bundle so that complete data were obtained in only 8

Electrocardiographic studies Electrocardiographic studies were carried out approximately 1 year after the operation as follows under pentobarbital anesthesia the heart was exposed via a horizontal transsternal incision at the fourth intercostal space Mechanical respiration was maintained through an A V R positive negative pressure respirator using pure oxygen Pericardial flaps were reflected to expose the surface of the ventricle and form a cradle for the heart Two pairs of electrodes were inserted into the anterior right ventricular myocardium perpendicularly to its surface One pair was positioned close to the septum and the other pair in the free wall in both apical and conus regions The electrodes were similar to those described previously[6] except that the individual points were situated at intervals of 3 mm along the shank of the electrode They were fastened securely in place by small plastic holders sewn to the epicardial surface The exact position of the electrode was verified anatomically at the end of the experiment A reference electrode was fastened to the surface of the left ventricle The exact positions of the electrodes from animal to animal could not be duplicated exactly but they were approximated as closely as the topography of the heart would permit The electrodes were rotated randomly to minimize small differences in their construction The right bundle was severed by introducing an iridectomy knife through the ventricular wall at the conus region close to the septum Completeness of the block was determined by the presence of a large positive deflection in the intramural and epicardial leads and a maximum negative deflection in the reference electrode and in Lead V_F An oscilloscope permitted monitoring of any two leads simultaneously Variations in unipolar potentials before and after right bundle branch block were recorded on a Hathaway five channel oscillograph modified as described previously The peak of R of each lead was measured along with the peak of R of the reference electrode using a Cambridge universal measuring machine Three complexes of each lead were measured and averaged Since the peak of R represents the time of arrival of the accession process at the electrode this time is somewhat shorter than the exact time of the onset of the intrinsic deflection Differences greater than 0 2 msec could be identified with certainty After the complexes had been measured the earliest point activated was extrapolated to zero time and all other measurements were corrected to this value

Results

The experimental data are shown in Table I and Figs 1 and 2

Table I Ventricular depolarization in experimental right ventricular hypertrophy and right bundle branch block

	Normal*	RBBB*	RVH	RVH + RBBB
Thickness (mm)	4 0	4 0	11 6	11 6
QRS interval in Lead V_F (msec)	44 1	89 2	48 0	96 8
Amplitude of epicardial R (mm N/20)	6 5	13 5	9 0	21 5
Subendocardial activation time (msec)	*8 5*	*24 3*	*10 4*	15 6
Transmural time (msec.)				
Earliest activated electrode	10 5	17 8	13 3	20 4
Latest activated electrode	9 0	9 4	16 7	13 0
Radial velocity (mm /sec)	354	225	983	569

Right ventricular hypertrophy alone The time required for completion of the excitation process at the subendocardial points of all four electrodes averaged 10 4 msec the range was 3 1 to 14 3 msec The earliest region activated was either apical close to the septum (5 animals) or apical away from the septum (6 animals) This is somewhat different from that found in previous experiments in normal animals Mural depolarization began 16 4 msec earlier than the peak of R in the left ventricular reference lead and was completed within 18 3 msec Corresponding times for the nonhypertrophied right ventricle in previous experiments were 16 7 msec and 9 4 msec for the beginning and completion of depolarization respectively There was a small difference in the time required for completion of mural depolarization between those regions that were activated first (13 3 msec) and those that were activated last (16 7 msec) In 2 dogs whose right ventricular myocardium was the thickest and whose ventricular pressure was the highest prominent Q-deflections were recorded from all points on the electrodes Septal and intracavitary potentials were recorded from only one of these however placement of the septal electrode was not satisfactory for accurate analysis Since the values for the individual items listed in the table did not differ significantly in the one animal with initial Q-deflections the data from this animal have been included in the table In the other animal records were not available for analysis

The amplitude of the R-deflection was noted to increase at all electrode points with right ventricular hypertrophy At the epicardial surface the average amplitude of R was 1 4 times greater than normal The velocity of mural accession at the earliest activated electrode was 983 mm per second with hypertrophy This is significantly different from normal in which case an intramural velocity of 354 mm per second was calculated from previous experiments

Right ventricular hypertrophy with right bundle branch block The average time of subendocardial depolarization from earliest to latest activated points after the right bundle was severed was 15 7 msec (range from 10 9 to 47 8 msec) twice greater than that of right ventricular hypertrophy alone but shorter than in uncomplicated right bundle branch block Regions to become activated first were the same as with hypertrophy Activation of the free wall began 26 7 msec later than the peak of R in the left ventricular reference lead It was completed within 18 2 msec as compared with 12 4 msec when right bundle branch block without hypertrophy was present There was a significant difference in the mural depolarization time between regions of early activation (20 4 msec) and those which were activated last (13 0 msec) When right bundle branch block was produced in the hypertrophied ventricle an increase in the amplitude of the R-deflection to 2 4 times its initial value was observed

Discussion

Right ventricular hypertrophy Ventricular depolarization is initiated by rapid spread of the excitatory impulse through the bundle of His its right and left branches and through the endocardial Purkinje plexus so that all endocardial points are activated nearly simultaneously Transmural spread follows[7] in nearly radial fashion at a lower speed as muscle units from endocardium to epicardium are activated in succession In the free wall it has been suggested that radial and tangential accession components[8] result from the differences in velocity of spread through the Purkinje network (1 5 to 2 0 M sec) and through the wall (0 370 M sec)[8] When the velocity of subendocardial spread is many times more rapid as in the normal heart radial components are larger than tangential and can be identified by the greater time required to activate successive points on an intramural electrode oriented perpendicularly to the surface of the heart Only the region activated last shows tangential components of significant magnitude resulting in nearly simultaneous activation of all points on the electrode at this site

In the present experiments in which the right ventricular wall attained a thickness of about three times normal the average time required to activate all subendocardial points was not significantly changed from normal (10 ...

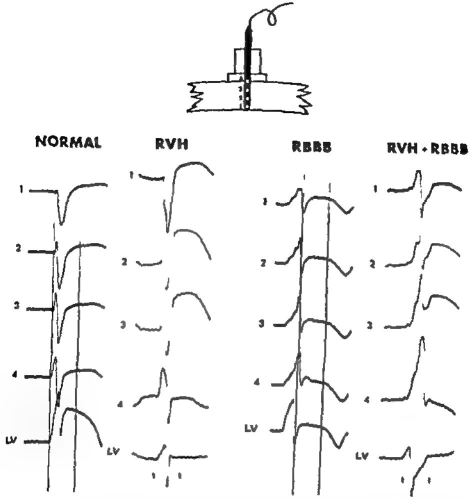

Fig 1 Unipolar potentials recorded from points 1 through 4 on an electrode placed in the apical region of the free wall of the right ventricle near the ventricular septum in two separate experiments *NORMAL* and *RBBB* were recorded from a dog without right ventricular hypertrophy in *RVH* and *RVH + RBBB* the right ventricle was about three times normal thickness Point 1 of the electrode is about 0 5 mm beneath the endocardium point 4 rests on the epicardium as depicted in the diagram The diameter of each of the electrode points is about 0 13 mm Note the initial R deflection at all points and the increased amplitude of R with hypertrophy Time lines are at interval of 0 1 second standardization is N/20

but the velocity of intramural spread was *nearly* trebled (983 *mm/sec* vs *354 mm/* sec $p < 0.001$) Thus even in the presence of a moderate degree of right ventricular hypertrophy the relative magnitude of radial accession components was maintained or even was increased Tangential components could not be identified even in those regions activated last The mathematical model already referred to (Reference 8) would have predicted tangential spread through the ventricular muscle due to the increase in intramural radial velocity contrary to what was observed This *analysis is valid apparently only for* any assumed but constant thickness of the ventricular wall When the thickness of the ventricular wall is increased slowing of the rate of Purkinje spread relative to the intramural velocity will not result in a greater tangential spread because any given epicardial point is closer to the wave front originating at a subendocardial point a short distance away than it is to the wave front which has barely started at a subendocardial point directly across the wall

from it. If the accession process permeates the ventricular muscle equally in all directions, the general wave front would be oriented radially, regardless of intramural velocities; furthermore, secondary Huygenian wavelets would be established.[9] These wavelets would be propagated at a greater velocity in the subendocardial regions and would be expected to approach the velocity of the initial wave fronts at the subepicardium. Experimental data have been published[10] which agree with this approximation. In uncomplicated right bundle branch block and in ventricular extrasystoles, wherein endocardial spread appears to be much slower, secondary wavelet formation would be abolished; hence a lower radial velocity of accession measured at the earliest point activated would be anticipated. A value of 225 mm./sec. is obtained in uncomplicated right bundle branch block; it is 569 mm./sec. in hypertrophy with bundle branch block.

Because of the increased velocity of intramural spread, the time of onset of the intrinsic deflection was earlier at the epicardial surface than would have been predicted on the basis of the increased thickness of the ventricular wall had the velocity remained unchanged. This observation suggests that measurement of the time of onset of the intrinsicoid deflection in precordial leads superjacent to the right ventricle would underestimate the magnitude of right ventricular hypertrophy, and that minor degrees of hypertrophy would not be recognized. On the other hand, even a slight delay in the time of onset of the intrinsicoid deflection would indicate a substantial degree of right ventricular hypertrophy. The fact that in these experiments radial spread was maintained in the presence of hypertrophy validates the use of this measurement, at least in degrees of hypertrophy up to almost three times normal thickness.

The cause of increased intramural velocity in right ventricular hypertrophy could not be explored in these experiments. It is apparent that it is due, at least in part, to some alteration intrinsic to the cell which arises as a consequence of the increased work load. In addition, it could result in part from the presence of secondary wavelets propagated at a greater velocity according to Huygens' concept.

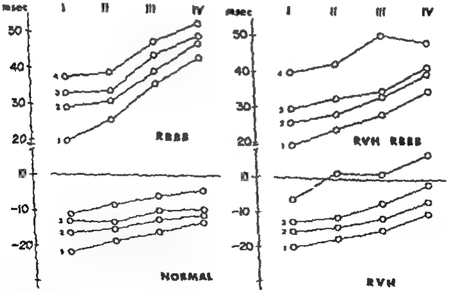

Fig. 7. Graph depicting the time of arrival of the accession process at points 1 through 4 of all electrodes plotted according to the order of activation of the first point (subendocardial). The 0 line represents the time of arrival of the accession process at the reference electrode in the left ventricle and all other values have been adjusted accordingly. The time is prefixed by a minus sign when the arrival of the accession process at the exploring electrode occurred earlier than that at the reference electrode.

Massive right ventricular hypertrophy in 2 animals resulted in the appearance of an initial negative deflection at all electrode points intramural and epicardial as well as in the right ventricular cavity in the one animal in which the tip of the exploring electrode entered the cavity Direct evidence which might be obtained from electrodes placed in the ventricular septum is lacking but the fact that an increased velocity of spread was observed in the thickened free wall suggests that similar changes in the accession velocity from right to left could occur in the hypertrophied septum leading to a diminution in the amplitude of the initial positive septal deflection An initial negative deflection could result from massive hypertrophy of the right side of the septum since our experiments show that the increase in velocity in the free wall is proportional to the degree of hypertrophy present Furthermore the portion of the septum activated from right to left is variable even in the normal dog [11] The idea that septal activation is altered in right ventricular hypertrophy has been suggested previously [3, 11, 13] From our experiments it would appear that the anatomically dominant ventricle influences the order of activation of the septum through alterations in the accession velocity There is no evidence from these experiments to support the hypothesis[14] that transmission of the excitatory impulse is delayed at Purkinje junctions in the presence of right ventricular hypertrophy uncomplicated by right bundle branch block

Right ventricular hypertrophy and right bundle branch block Spread of the accession wave in the free wall of the right ventricle in uncomplicated right bundle branch block has been shown to be radial at the regions activated early and tangential at all others due to failure of rapid spread of the excitation impulse to all endocardial points Even though subendocardial spread seemed to be somewhat more rapid when right bundle branch block was complicated by right ventricular hypertrophy (15 6 msec vs 24 3 msec $p < 0.02$) no other aberration in the form of QRS was noted except for a greater increase in the amplitude of R at all electrode points principally at the epicardial surface deflection was increased approximately 40 per cent above normal with hypertrophy alone The increase was greater (140 per cent) in combined hypertrophy and block than with right bundle branch block alone An increase in the total active cross sectional area of the right ventricular muscle mass activated at a given moment would account in part for the increased amplitude of the R deflection in hypertrophy with and without right bundle branch block There is evidence which indicates that the resting membrane potential and the action potential are not increased in the hypertrophied muscle cell [15] Our observations support the idea that when hypertrophy is present in combination with right bundle branch block an increased amplitude of the terminal R deflection results Similarly a greater prolongation of the QRS interval in Lead V_F was seen when right bundle branch block was complicated by right ventricular hypertrophy than in right bundle branch block alone (96 8 msec vs 89 2 msec $p < 0.02$) The prolongation of the QRS interval due to hypertrophy as compared with normal (48 0 msec vs 44 1 msec) was also significant ($p < 0.05$)

Summary

Ventricular depolarization was studied in 12 dogs in which the thickness of the right ventricle was trebled by the production of supravalvular pulmonary stenosis Intramural electrodes were used to record the variations in potentials at four points from subendocardium to epicardium in four anterior regions of the free wall of the right ventricle conus region near the septum conus region away from the septum at the apex near the septum and at the apex away from the septum Right bundle branch block was produced by the severance of the right branch of the bundle of His in 8 of the animals with right ventricular hypertrophy

In right ventricular hypertrophy uncomplicated by bundle branch block the accession wave spread from subendocardium to epicardium in radial fashion at a velocity nearly three times as great as that in normal animals Tangential components were not in evidence even at the electrode last activated as is seen normally The

velocity of subendocardial spread was not significantly altered In 2 animals an initial Q-deflection was observed in the right ventricular cavity in the free wall and at the epicardial surface of the right ventricle Its origin was attributed to an increased velocity of accession in the right side of the septum during the time that the wave travels from right to left

When right bundle branch block was superimposed on right ventricular hypertrophy the spread of accession was similar to that observed in uncomplicated right bundle branch block It was radial in the regions activated early and tangential in regions activated late In addition the amplitude of the R deflection at the epicardial surface which is somewhat greater in uncomplicated hypertrophy than in normal conditions was greatly increased in right bundle branch block alone Also the QRS interval measured in Lead V_F was slightly increased in hypertrophy alone and was significantly increased in combined block and hypertrophy as compared with block alone

The data from these experiments provide clues to the basic understanding of the electrocardiographic changes which occur in man with right ventricular hypertrophy with and without right bundle branch block

We are indebted to Miss Patricia M Teel and Mrs Imogene Lister for their assistance and to Dr Thomas D Hodges and Dr Lloyd E Rader Jr who performed some of the initial surgical procedures

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A high-speed camera for high-frequency electrocardiography

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There are high frequency components of 1,000 cycles per second or more in the electrocardiogram.[1-10] It has been shown repeatedly that these high frequency components are more common in patients with coronary heart disease than in normal control subjects.[3,6,8,9] Thus far, one of the problems in recording such electrocardiograms has been the lack of a method which was both inexpensive and satisfactory to display these high frequency events. It is the purpose of this paper to describe a relatively simple and inexpensive method for recording and displaying these phenomena.

To obtain a continuous sequence of P-QRS-T complexes with an expanded time scale requires a continuous motion camera. A still camera is inadequate. Commercially available continuous cameras use 35 millimeter film and cost $1,000 or more for the camera alone. The method to be reported here uses 16 millimeter film, an inexpensive standard home movie camera converted for continuous motion, and a microfilm viewer. This equipment costs approximately $350 for both the modified camera and a very convenient instrument to display the electrocardiogram so recorded. The other requirements for high fidelity electrocardiography, namely, a wide band, high gain preamplifier and a cathode ray oscilloscope, are already available in many diagnostic centers and research laboratories throughout the world.

Method

A Paillard Bolex (No. 34664) 16 mm. motion picture camera was converted to a continuous motion camera by the following steps. (A Bolex Model H16M is currently available and would be suitable for conversion.) The shutter and pulldown claw were removed. These changes allow the film to run smoothly and continuously. In order to keep the film moving flush with the aperture plate, two rollers 20 millimeters in diameter—one designated the upper roller, which measured 7.5 mm. in width, and the other designated the lower roller, which measured 8 mm. in width—were mounted so as to rotate freely on the pressure pod support spindle. In order to mount the upper roller it was necessary to reduce the width of the pressure pod support arm by 6 mm. This allowed the film to run over these rollers on to the lower film sprocket.†

Fig. 1 illustrates the internal part of the camera and shows the previously described rollers in place.

The slowest speed of the camera was 8

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†For designing and helping in the mechanical conversion of this camera, we wish to thank Mr. Charles Huett, former Technical Sales Representative, Paillard Inc., 100 Sixth Avenue, New York 13, N. Y.

frames per second and when it was converted to continuous motion the equivalent film speed was 80 mm per second Since a slower speed was desired the governor springs were bent slightly in order to obtain a speed of about 50 mm per second Although it is necessary to run the converted movie camera slowly it must also be run evenly If the speed is too slow for a given camera there is a tendency for the film to move unevenly The speed of the film and the steadiness of the trans

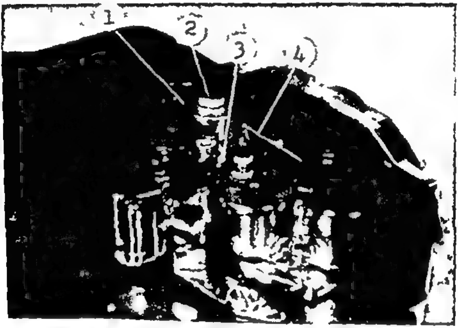

Fig *1* Interior view of camera showing changes made The shutter and pulldown claw have been removed Other changes have been numbered in the figure as follows (*1*) upper roller (*2*) cap screw in spindle that supports pressure plate assembly (*3*) lower roller (*4*) portion of pressure plate assembly where a section is cut away to make room for upper roller

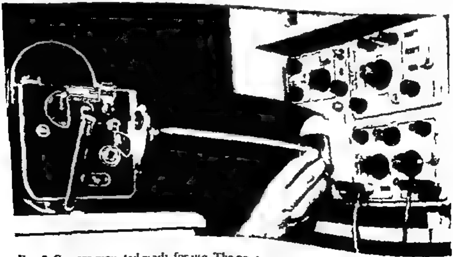

Fig *2* Camera mounted ready for use The positioning and de... being held on the face of the oscilloscope The piece of dark paper fastened to the bezel of the oscilloscope ... half of a cone that should be ... most of the incident light

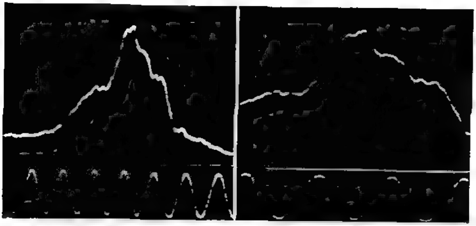

Fig 3 Two photographs of a notched abnormal QRS complex These are enlargements made of the 16-mm motion picture film The lower line is a 60-cycle ine wave introduced on the second beam of the oscilloscope The motion picture film was moving 5 0 cm per second in the first picture and 11 5 cm per second in the second picture Much faster peed can ea ily be obtained At the higher speed the notches are not so clear and harp although for recording some phenomena this higher peed may be needed

port can be checked by photographing a 60-cycle test signal on the oscilloscope This test signal is readily available in most oscilloscopes If not a 60-cycle signal usually can be obtained by using an antenna which consists of a wire connected to the positive pole of the Y input If the film is run too fast the complexes become broader than necessary and the identification of notches and slurs is not facilitated

The camera should be focused so that the full width of the film is used In order to focus at this short distance using a lens with a focal length of 25 mm a washer approximately 1 mm in thickness was placed between the lens and the body of the camera The correct distance for focusing was found to be 30 cm To facilitate rapid and accurate focusing the following device was made A ⅜ inch dowel was placed in a hole drilled in the center of the flat surface of a block of wood which measured 2 by 2 inches The over all dimension from the tip of the dowel to the base of the wood block was 30 cm With the 2 by 2 inch block of wood placed on the face of the cathode ray tube it was simple to set the distance quickly and center the lens with the pointed end of the dowel

Fig 2 shows the mounted camera focusing device and oscilloscope A light protective cone which is half cut away is also shown

In order to photograph the trace the amplitude of the QRS complexes was adjusted to be 6 to 8 cm in height on the face of the cathode ray oscilloscope Then the oscilloscope sweep was stopped and the resulting trace was centered on the face of the cathode ray tube The motion of the oscilloscope trace must be at right angles to the long axis of the film The camera is mounted on a tripod or other convenient support The cathode ray oscilloscope is turned on its side and the electrocardiogram is obtained by photographing the oscillation of the light spot on the Y axis of the oscilloscope

The intensity of the beam was adjusted so that it gave a bright line with little or no halo The aperture was set at f 2 The camera was run until the desired number of complexes had been photographed A little experience will quickly eliminate any exposure problems Since there is no shutter in the camera the first 6 to 18 inches of film will be fogged at the beginning of the run Unless a very dimly lit room is used a black paper cone must be used between the bezel of the oscilloscope and the camera A small hole may be cut out of the cone for inspection of the oscilloscope

The film may be viewed by using either a 16 mm enlarger or a standard microfilm viewer to obtain a projection that is large enough for examination and study In

either instance prints as large as desired usually 2 to 6 inches high can be made by the usual darkroom technique (see Fig 3)

Summary

A method for converting an inexpensive motion picture camera to a continuous motion camera has been described This is invaluable for recording high frequency events of short duration which require an expanded time scale Examples of such recordings are high fidelity electrocardiograms and their first derivative with respect to time

We wish to thank Mr Harry L Fies for his invaluable assistance

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Case reports

Increased serum acid phosphatase after arterial embolism

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In previous papers we reported the occurrence of acid hyperphenylphosphatasia during the acute stages of myocardial infarction, pulmonary embolism, and peripheral thrombophlebitis.[1,2] The present communication reports a similar phenomenon in a case of recurrent systemic arterial embolism.

Case report

The patient was a 58-year-old Negro woman who was admitted to the hospital with a 3 year history of exertional angina and dyspnea and a 3 day history of progressive worsening of these symptoms. There was no history of hypertension or diabetes. On admission the blood pressure was 140/90 mm. Hg, the pulse was 90 per minute and regular, and the respirations were 16 per minute and quiet. The neck veins were distended, and there were a few moist rales in both lung bases. Examination of the heart revealed an accentuated pulmonic second sound and a Grade 2/4 mid-systolic blowing murmur which was loudest at Erb's area. The liver and spleen were not palpable, and there was no peripheral edema. The femoral pulses were strong and equal, the popliteal pulses were weak bilaterally, and the dorsal pedal and posterior tibial pulses were absent bilaterally. The electrocardiogram showed normal sinus rhythm, left bundle branch block, left ventricular hypertrophy, and small Q waves in Lead I, aVL, and V_1, suggestive of anteroseptal myocardial infarction of indeterminate age. Subsequent electrocardiograms were unchanged. The chest x-ray film showed enlargement of the cardiac apex downward and outward, compatible with left ventricular hypertrophy, and mild bilateral hilar prominence, suggestive of mild left ventricular failure. The blood count, fasting blood sugar, blood urea nitrogen, urinalysis, and serial serum glutamic oxalacetic transaminase activities were within normal limits. With bed rest, digitalis, diuretics, and a low salt diet, her clinical state improved.

On the fourth hospital day, severe pain and exquisite hypersensitivity developed in the entire right lower extremity. The right femoral pulse was no longer palpable, and pallor of the sole of the right foot was observed. A critical level of temperature appeared at the junction of the middle and upper third of the right thigh. A diagnosis was made of embolism to the right common or external iliac artery. Shortly thereafter, the right femoral pulse again became forceful, and the critical level of temperature shifted to the midthigh. It was thought that the embolus had dislodged and moved distally. The patient was then transferred to the operating room for embolectomy. At operation a 3 by 0.4-cm. embolus was removed from the distal portion of the common femoral artery at the point of its bifurcation into the superficial and deep femoral arteries. The right popliteal artery was explored and found to be patent. Postoperatively, the critical level of temperature moved to the region of the knee, and pain and hypersensitivity in the foot continued despite anticoagulation. Presumably, small residual emboli were still lodged distally. Over the next 12 days her symptoms gradually abated, the plantar pallor and coldness of the right foot progressively waned, and the patient began to ambulate. Necrosis of tissue did not occur.

On the thirteenth hospital day, while anticoagulated, the patient became aphasic and lapsed into stupor. At the same time, the right foot became cold, edematous, and pale. The femoral pulses remained full and equal. A spinal tap revealed blood-tinged xanthochromic fluid under normal pressure with a protein content of 3?5 mg. per cent. Motor power and the reflexes were unimpaired. A diagnosis was made of recurrent embolism to the brain and

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to the right lower extremity below the knee probably due either to a mural thrombus in the left ventricle at the site of previous myocardial infarction or to nonbacterial thrombotic endocarditis The aphasia and mental clouding slowly cleared over the next several weeks The right foot however underwent progressive dry gangrene and she was again transferred to the operating room for amputation

Serum acid phenylphosphatase activities The serum acid phenylphosphatase activities (SAPP) were determined almost daily over a period of 4 weeks on freshly drawn morning specimens of blood using the Gutman modification of the King Armstrong technique[4] and observing the precautions described previously[1] Aliquots of the same sample of serum differed by no more than 0 1 units from each other Grossly hemolyzed samples of serum (pink tint) were discarded The substrate solution of sodium phenylphosphate was prepared fresh at intervals of 2 to 5 days In our laboratory the

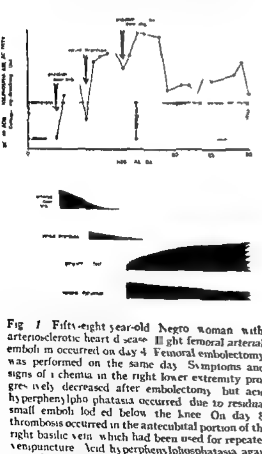

Fig 1 Fifty-eight year-old Negro woman with arteriosclerotic heart disease Right femoral arterial embolism occurred on day 4 Femoral embolectomy was performed on the same day Symptoms and signs of ischemia in the right lower extremity progressively decreased after embolectomy but acid hyperphenylphosphatasia occurred due to residual small emboli lodged below the knee On day 8 thrombosis occurred in the antecubital portion of the right basilic vein which had been used for repeated venipuncture Acid hyperphenylphosphatasia again ensued Organization of the thrombus into a thin fibrotic cord proceeded over the following week On day 13 arterial embolism occurred to the brain and to the right lower limb below the knee Acid hyperphenylphosphatasia once more appeared Cerebral dysfunction slowly waned but gangrene of the right foot steadily progressed necessitating eventual amputation

normal SAPP range for women is 0 3 to 1 6 Gutman King Armstrong units

The first specimen of blood was drawn on the fourth hospital day approximately 3 hours after the onset of pain and before embolectomy was performed the SAPP on this specimen was 0 4 units On hospital days 5 6 and 7 the SAPP progressively climbed to 2 3 units and then on the eighth day it fell back to 1 0 units

On the eighth hospital day thrombosis occurred in the antecubital portion of the right basilic vein at the site of repeated venipuncture The thrombosed segment of vein measured [illegible] 3 by 2 0 cm Resolution and organization of this thrombus proceeded over the following week or so On hospital days 9 through 12 immediately subsequent to this episode of venous thrombosis and during which time the symptoms and signs of ischemia in the right lower limb had progressively decreased almost to the vanishing point the SAPP as determined in samples of blood obtained from the right basilic vein central to the site of thrombosis steadily climbed to 3 3 units

On the thirteenth hospital day recurrent arterial embolism occurred to the right lower extremity and to the brain A specimen of blood drawn a few hours after onset of symptoms had a SAPP of 2 7 units a fall from the level of 3 3 units on the previous day Subsequently on hospital days 14 through 18 the SAPP rose to a height of 3 9 units

Thereafter on hospital days 19 through 30 the SAPP fell and leveled off to 1 8 to 2 9 units This period correlated with the occurrence of progressive gangrene of the right foot and with the resolution of cerebral dysfunction incident to the cerebral embolism

These changes in serum acid phenylphosphatase activity are diagramed in Fig 1

Discussion

In each of the episodes of thromboembolism observed in this patient the onset of acid hyperphenylphosphatasia followed the onset of symptoms by several hours reached a peak 48 to 72 hours later and lasted 3 to [illegible] days This pattern is similar to that noted after some cases of myocardial infarction[1] and suggests a common pathogenesis

As described previously[1] we have entertained several possible explanations for the acid hyperphenylphosphatasia of thromboembolism (a) degeneration of enzyme rich parenchymal tissue subserved by the occluded vessel (b) autolysis of enzyme rich cells (particularly erythrocytes and platelets) enmeshed within the blood clot (c) generalized hypoxic injury to (with consequent release of enzymes from) all body organs—but particularly the prostate liver spleen kidney and marrow—caused by an associated hypote

and shock, (d) thrombocytosis caused by stress-induced splenic contraction and by increased thrombocytogenesis due to tissue necrosis. Arguments have already been presented against the first three of these possibilities,[3] and the present case provides further evidence against the first. Thus, on hospital days 9 through 12, the serum acid phenylphosphatase activity progressively increased to high levels, whereas objective and subjective evidence of ischemia in the right lower extremity had been steadily decreasing since day 4 and had by day 12 almost disappeared. Again, during hospital days 19 through 30, overt gangrene of the foot was progressively increasing in extent, yet the serum acid phenylphosphatase activities were much lower than on days 14 through 18 immediately after the embolism. Finally, acid hyperphenylphosphatasia occurred after thrombosis of a small segment of the right basilic vein, but in this instance there was no edema, ischemia, inflammation, or necrosis of extravascular tissue.

All this is not to deny that degenerating parenchyma subserved by an occluded artery or vein may make some contribution to the acid hyperphenylphosphatasia. Indeed, the high phosphatase activities noted on days 19 through 30 coincided with progressive gangrene of the right foot and presumably were caused by a combination of necrosis of bone and soft tissue in the foot and/or progressive thrombosis of vessels distal to the site of embolic occlusion.

Summary

A case is described of a 58-year-old Negro woman with arteriosclerotic heart disease who successively developed arterial embolism to the right lower extremity with transient ischemia of the limb, thrombosis in the right basilic vein caused by repeated venipunctures, and simultaneous recurrent arterial embolism to the right lower extremity with gangrene of the foot and to the brain with symptoms and signs of cerebral infarction. The emboli presumably originated in the heart.

Serial serum acid phenylphosphatase activities were determined almost daily throughout this 4 week period. Starting from a basal level of 0.4 Gutman-King-Armstrong units, acid hyperphenylphosphatasia which lasted from 3 to 6 days and reached a maximum of 2.3, 3.3, and 3.9 units, respectively, was noted after each of the three episodes of thromboembolism.

A similar phenomenon has been noted after acute myocardial infarction, pulmonary embolism, and thrombophlebitis, and presumably a common mechanism is involved in all thromboembolic diseases. The nature of this mechanism is not at all clear, although thrombocytosis is conjectured to play an important role. The available evidence indicates that autolysis of erythrocytes and platelets within the blood clots themselves may also contribute to the serum acid phenylphosphatase activity. Release of the enzyme from parenchymal tissue injured by ischemia or inflammation may also occur but is not essential.

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Single coronary artery

A report of two cases

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A single coronary artery is a rare congenital abnormality. Smith[6] reviewed the literature and discussed the 43 cases reported to 1950. He discarded two as not being true cases and added two of his own, leaving the total unchanged at 43. Longenecker and associates reviewed the 25 new case reports which had appeared in the literature after 1950 and added two more cases of their own, thus bringing the total to 70 cases. The only case seemingly overlooked by Longenecker and associates was the one reported by Ramirez.[3] This last example was found in a 65-year-old Negro woman who had been hospitalized several times for hypertension and renal insufficiency. At necropsy the heart weighed 430 grams; it showed no opening or dimpling in the left aortic sinus, and a single coronary orifice 4 mm in diameter arose from the right aortic sinus. This divided into two major branches, each of which then followed the usual distribution of the right and left coronary arteries, i.e. it was an example of Type 2 in Smith's classification. Transverse sections of all the main stems failed to show any disease of the arteries, and the myocardium showed no evidence of fibrosis. The cause of death was chronic glomerulonephritis.

The above mentioned case of Ramirez, together with the two now reported by us, raises the total to 73.

Case reports

Case 1. The patient was a 34-year-old Bantu woman of the Zulu tribe. On April 15, 1958, the patient was admitted to Edendale Hospital, Pietermaritzburg, Natal, in extremis with a blood pressure 70/[illegible] mm Hg and comatose. The diagnosis was hemoptysis with an acute tuberculous condition of the left lung and right pleural effusion. The patient died on April 20, 1958, and a necropsy examination was performed the next day.

Necropsy findings (No. 1741/58). The patient was well built, with a weight of 150 pounds, which certainly was not the picture of a chronic phthisis. A small amount of fluid was found in the right chest cavity, with the pleura studded with tubercles and with the lung completely solid with a tuberculous pneumonia breaking down into cavities, especially in the lower lobe; the hilar glands on the right side were large and caseous; the picture was one of phthisica florida, a primary infection. Spill-over infection was present also in the left lung. Tuberculous ulcers were present in the small intestine and the liver showed marked fatty change. The heart was fatty and flabby; the gross weight was 234 grams. On inspection the right coronary orifice, 5 mm in diameter, was found in the normal position. No trace could be found of a left coronary orifice, not even a dimple in the left aortic sinus. A cannula was tied into the first 3 mm of the right coronary artery and the vessel was perfused with radiopaque material, after which the heart was opened and photographed much in the manner originally described by Schlesinger.[4]

Fig. 1 is the diagram of this heart. The pattern does not readily fall into any of the three classes suggested by Smith; probably it comes nearest to being a Class I pattern; on the right side the pattern is within normal limits except that the conus branch is very large, extending over the intraventricular septal bed into the apical area of the left ventricle

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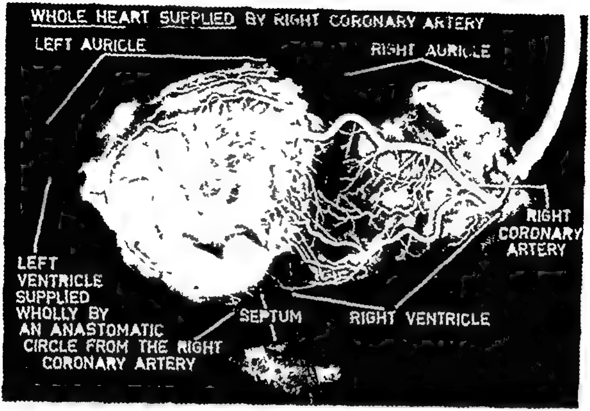

Fig. 1. Zulu female with coronary artery present only on right side of heart.

The supply to the left side bears no relation to the distribution normally seen with the left coronary main stems; the left ventricle was supplied with blood from a vessel running in a semicircle from the right conus branch at the left apex to the right main coronary stem along the line normally followed by the left circumflex artery. This picture is of especial importance in that it shows how a radiologically poor anastomotic circulation is adequate in life. Subsequently, dissection of the right coronary artery showed it to be free from any disease and the myocardium showed no abnormality on microscopic examination.

Case 2. The patient was a 60-year-old white British male.

The patient was admitted to Perth Chest Hospital, Western Australia, on Oct. 16, 1961, with a [illegible]-month history of malaise and weakness and abdominal pain of 1 month's duration. On admission to hospital he was found to be wasted; enlargement of the liver and spleen were noted; the total white cell count was within normal limits but the differential count showed a high proportion of mononuclear cells. A gland biopsy showed lymphosarcoma. In spite of appropriate treatment, the condition of the patient steadily deteriorated and he died on Dec. 24, 1961.

Necropsy findings (No. 39?/61). The body was emaciated and showed multiple purpuric and petechial hemorrhages. A tumor mass was present

Table I. Age of patient at time of death

Sex	Fetus or infant	Child (– 19 yr.)	Adults			Total
			20-39 yr.	40-59 yr.	60 yr. and over	
Male	11	1	8	8	11	39
Female	11	1	4	[illegible]	6	28
Total	[illegible]	[illegible]	12	14	17	67

*Two more cases in children but sex not given.

Fig 2 White British male with a coronary artery present only on the left side of heart

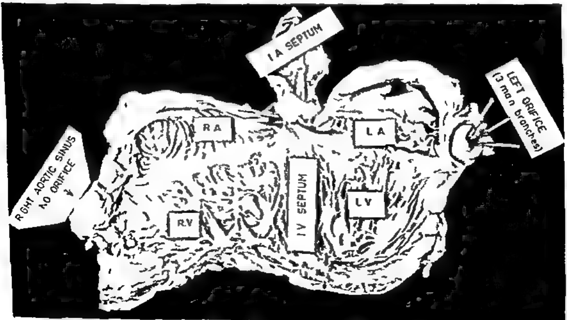

Fig 3 Naked-eye view of internal aspect of heart of Case 2 showing only a left coronary orifice

in the tail of the pancreas and the spleen showed multiple pale areas There was also diffuse tumor infiltration along the spine at the base of the left lung with gross mediastinal glandular enlargement and gross tumor invasion of the left lung The left kidney also showed tumor infiltration Subsequent microscopic examination showed all the tumor masses to be lymphosarcoma At necropsy the heart weighed only 260 grams The left *coronary orifice* appeared to be normal with no local atherosclerosis of the aortic bulb the orifice measured 5 mm in *diameter and was found in the normal position in* the left anterior sinus of Valsalva with no trace whatever of the right coronary orifice (see Fig 3) The heart was processed by the same technique as that used in Case 1 it should be noted that in one important detail our technique[1] differs from that of Schlesinger in so far as we cannulate separately through the ostia of each of the three to five main stems of the coronary arteries This is shown in Fig 2 the skiagram of this second heart The skiagram shows that on the left side the coronary artery *has three main stems one of them being a good* example of a third main primary division These three main stems follow a normal pattern and the blood supply to the right ventricle is by simple extension of the left circumflex branch along the course normally followed by the main stem of the right coronary artery i e this would also fall into Class I of Smith s classification Subsequent dissection of the coronary arteries showed no significant disease and microscopic examination of the myocardium also showed no abnormality

Discussion

With the exception of the single case of *Ramirez*[3] *detailed above all previous* cases have been adequately reviewed first by Smith[6] and subsequently by Longenecker and associates *Therefore it is only* necessary to consider a few points arising from our two cases Our first patient a *Zulu woman was married with two children* and had worked hard in the fields all her adult life as is the Zulu custom yet her *left ventricle had been nourished by an* arterial system which appears on the skiagram to be rather faint and poorly filled *This provided a good standard by which* we could assess the likely functional efficiency of coronary interarterial anastomoses by the injection techniques *Similarly the* 60-year-old white man (our Case 2) did not seem to have suffered any disability from having only *one coronary artery for* the first 30 years of his adult life he had been a professional foot soldier and during the last 13 years of *his life he had worked* hard as a farmer in Australia This is the general finding i e that the presence of only one coronary artery *does not produce* any significant disablement and is compatible with a long full life the oldest case reported is that of an 83 year-old woman *Table I shows the* grouping of the patients by sex and age at death in the 67 published cases including our own for which satisfactory details are available of the other six patients there were three for whom no age was given and three including two children for whom no sex was given

The high proportion of deaths in infancy was thought by the various authors to be due to the presence of other cardiac anomalies Of the 43 patients who survived to adult life there were 15 who died of cardiac disease i e the presence of a single coronary artery does not seem seriously to increase the possibility of death from cardiac disease A review of the case histories of the published cases shows that in those age groups at risk atherosclerosis is surprisingly mild but the numbers are too few for this to have any significance

Summary and conclusions

The occurrence of single coronary arteries in two individuals is reported and brief details are given of the findings in the 73 cases which have appeared so far in the literature It would seem that in the ab*sence of other cardiac abnormalities the* presence of a single coronary artery is not associated with cardiac disability or de*creased life expectancy*

These notes are published with the permission of the Commissioner of Public Health Western Aus*tralia The photography is by the* Medical Photographic section of the Public Health Department Western Australia We are indebted to Professor Saint of the University of Western Australia for permission to publish details of Case 2

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Special article

Relationship of dentistry to cardiology

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Although physicians are aware of the importance of good dental care and oral hygiene for maintaining health, there is a tendency to leave the problem of seeking and obtaining dental advice and care to the patient. However, there are many reasons why physicians, and in particular cardiologists, should be more active in advising patients to maintain excellent oral hygiene and dental health and in urging those with poor dental hygiene to obtain satisfactory dental care. The lack of interest of cardiologists in problems related to dentistry is evident when one considers the rarity of papers related to this subject in journals of cardiology and the lack of attention to the dental health of the patient in the teaching and practice of medicine.

The purpose of this presentation is to discuss the relationship and importance of dentistry to cardiology, as well as to demonstrate the need for early and constant care of the teeth not only in the patient with heart disease but in any patient with chronic disease. Although the concepts are presented from the point of view of the cardiologist, they apply to all physicians.

Dental pathology

It is not within the scope of this paper to discuss dental pathology in detail; however, for purposes of orientation, as well as to illustrate the extent of dental diseases, a partial classification of dental diseases is presented in Table I. By far the conditions of greatest concern to the cardiologist are those which involve infection of the oral tissues, primarily dental caries and periodontal disease. The importance of these diseases is twofold. First, they may give rise to serious systemic disease, and second, they take the patient with heart disease to the dentist's office. As indicated below, dental procedures in patients with serious cardiac disease may be associated with a certain degree of risk to cardiac health and to the life of the patient.

It is important to understand the mechanisms by which dental infections may progress to become a source of serious systemic disease.[1] The least complicated form of tooth infection is known as dental caries. In this condition the enamel is demineralized and the dentin is invaded by bacteria, which produces destruction of these tissues. Although a carious tooth may be painful under ordinary conditions, it does not present a threat to general health. However, after trauma to the face, infected fragments of a carious tooth may be aspirated into the lungs, which results in pulmonary abscess or pneumonia. Fur

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Table I

1. Anomalies of dentition
   - Anodontia vera
   - Pseudo-anodontia
   - Partial anodontia
   - Retained and impacted teeth
   - Pericoronal infection
   - Supernumerary teeth
   - Abnormalities of occlusion
2. Developmental defects
   - Hypoplastic defects
   - Dystrophy of congenital syphilis (Hutchinson's teeth)
   - Mottled teeth
3. Functional changes
   - Attrition
   - Abrasion
   - Erosion
4. Traumatic disease
   - Occlusal trauma
   - Concussion and luxation
   - Fracture
5. Dental caries
   - Acute caries
   - Chronic caries
   - Root caries
6. Pulp infection
   - Hyperemia of pulp
   - Acute pulpitis
   - Chronic pulpitis
7. Dento-alveolar abscesses
   - Suppurative periodontitis
   - Chronic apical periodontitis
   - Subperiosteal abscess
   - Gingival abscess
8. Periodontal disease
   - Periodontal atrophy
   - Atrophy of disease
   - Traumatic atrophy
   - Gingivitis
   - Marginal gingivitis
   - Hypertrophic gingivitis
   - Marginal periodontitis
   - Periodontosis

thermore, unless dental carious processes are interrupted by operative dentistry, the dental pulp will almost surely be invaded by pathogenic microorganisms. The resulting pulpitis is usually followed by periapical involvement through the egress of the products of infection by way of the apices of the root. As the infection progresses, this apical lesion becomes more severe and suppuration may occur with the development of dento-alveolar abscess. As a result of involvement of the dental pulp (pulpitis) and the periapical tissues, bacteria are brought into proximity with blood vessels and lymphatics and thereby have access to the systemic circulation to cause bacteremia, septicemia, and associated complications such as subacute bacterial endocarditis. In addition, as the teeth function in mastication they undergo a plunger-like action which serves to force bacteria into the circulation.

Dental caries is not the only process which may result in disease of the supporting structures of the teeth. The soft tissues and alveolar bone which support the teeth (periodontium) may become infected by agents which enter at the free margin of the gingivae. Local factors such as dental calculus, food impaction, and traumatic occlusion, when left uncorrected, will contribute substantially to the destruction of the dental ligament. The overlying infection, which may be primary or secondary, can certainly further this degenerative process which eventually leads to the formation of deep pockets of infection around the teeth. If the infection and irritation remain untreated, suppuration and even periodontal abscess may develop. Underlying systemic disease, particularly diabetes mellitus, may markedly accelerate the degenerative process. The over-all result of this syndrome is that concentrations of pathogenic organisms are present in an area of degenerating tissue. During the trauma of dental procedures, mastication, or brushing of the teeth, bacteria may invade the blood stream from these infected areas in the periodontium.

Dental aspects of specific cardiac diseases

Congenital heart disease. Extraction of infected teeth may be followed by intense bacteremia.[4] The risk of development of subacute bacterial endocarditis after extraction is greater in patients with congenital heart disease than it is in patients with normal hearts, not only because of the cardiac defect itself but also, in some cases, because of changes in the periodontal structure associated with congenital heart disease.[8] Among the various types of congenital cardiac defects the potential for the development of subacute bacterial endocarditis is highest in ventricular septal defect and patent ductus arteriosus.

Bacterial endocarditis has also been

observed to follow simple dental manipulations such as the filling or cleaning of teeth.[6] Most periodontal procedures have been shown to result in bacteremia, the degree of which is related to the intensity of the trauma.[7]

Subacute bacterial endocarditis may occur without extraction or therapeutic dental manipulation in patients with congenital heart disease who have periodontal infection and disease. Although it is difficult to establish that the infected teeth are a source of the bacteremia, it is known that *Streptococcus viridans* is a common cause of chronic pulpitis. Indeed, positive blood cultures have been reported after brushing of the teeth[8] or after the chewing of a resistant mass.[9]

Patients with cyanotic congenital heart disease frequently have changes in the periodontal tissues which predispose to poor oral hygiene and chronic periodontal infection.[6] The most characteristic changes in the periodontal tissues consist of dilatation of the gingival capillaries which results in edema of the gums and decreased resistance to infection. The dilatation of the gingival capillaries is thought to be a result of increased salivary kallikrein. Frequent infections of the upper respiratory tract, loss of lip seal, and mouth breathing expose the periodontal tissues to bacterial attack. In the presence of lowered resistance of the periodontal tissue, even normal oral flora may establish infection.

In patients with coarctation of the aorta, the mandibular arteries as well as the arteries leading to the individual teeth may be enlarged. Tooth extraction in such patients may result in excessive bleeding.

Rheumatic heart disease. Rheumatic valvulitis and scarring of the cardiac valves predispose these structures to infection with bacterial organisms, especially *Streptococcus viridans.* The same relationships between infected teeth and subacute bacterial endocarditis as noted above for patients with congenital heart disease apply to patients with rheumatic heart disease.

Arteriosclerotic heart disease. Dental care in patients with arteriosclerotic heart disease presents special problems. Such patients are in the older age groups and may require extensive dental therapy. The pain, anxiety, and fear associated with dental procedures may be deleterious to patients with coronary sclerosis and ischemic heart disease. Tachycardia, angina pectoris, and even myocardial infarction may follow even mild emotional stimuli.[10] Therefore, good oral hygiene is important to patients with arteriosclerotic heart disease. Poor teeth or poorly fitted dentures may result in dietary inadequacies and vitamin deficiency, particularly in older patients. The inadequate dietary pattern may lead to depression and other psychological disturbances in old people. Infected teeth or periodontitis has been implicated in the development of suppurative arthritis, uveitis, iritis, neuritis, fibrositis, cholecystitis, thrombophlebitis, pyelonephritis, cavernous sinus thrombosis, and even in some cardiac arrhythmias. Thus, despite the potential hazards of dental therapy to patients with arteriosclerotic heart disease, in the interest of total care of the patient such persons should be urged to seek and continue with adequate dental care.

Patients with arteriosclerotic heart disease who have had a previous myocardial infarct may be receiving anticoagulants. Although isolated instances of excessive bleeding after tooth extraction in patients receiving anticoagulants have been reported,[11] there seems to be little risk of bleeding after tooth extraction in patients whose prothrombin time is allowed to decrease to the lower limits of the recommended therapeutic range.[1] It is the responsibility of both the physician and the dentist to be certain that the prothrombin time is not excessively prolonged and that the determination of prothrombin levels is obtained accurately. Furthermore, after extractions the dentist or oral surgeon must take steps to encourage local clotting. Before recommending a reduction of the prothrombin time to normal in preparation for tooth extraction, the physician should consider the risks associated with interruption of prolonged anticoagulant therapy and the rebound phenomenon.[12,13]

Patients with arteriosclerotic heart disease may be receiving digitalis, quinidine, or procaine amide. Any of these drugs may lower the threshold of the vomiting

and care must be taken not to stimulate this reflex during dental manipulation

Although local anesthesia is generally used when anesthesia is required extensive dental procedures or control of difficult patients may necessitate the use of a general *anesthetic agent* Because of their effect on myocardial function the use of anesthetic agents especially general anesthetic agents in patients with serious cardiac disease involves a certain degree of risk[1] It is not the purpose of this paper to discuss the merits of any one anesthetic agent in patients with cardiac disease However in order for the anesthetist to choose the most ideal anesthesia for a particular patient he must be fully aware of the nature and extent of the patient s cardiac disease Thus there must be free communication between the dentist oral surgeon anesthetist and cardiologist

Hypertensive cardiovascular disease Dental therapy in patients with hypertensive cardiovascular disease is relatively safe However as in patients with arteriosclerotic heart disease fear pain and anxiety may result in detrimental cardiovascular reactions In this regard some forms of hypertension have a strong psychoneurogenic component[16] It is not inconceivable that in some patients with hypertension the expectation of a visit to the dentist may act as a conditional stimulus which *results in further elevation of the arterial* blood pressure This phenomenon is well known to physicians as is the fact that in some patients the arterial blood pressure recorded in the physician s office may be considerably higher than blood pressures recorded in the patient s home[17]

Despite elevated arterial blood pressure hemorrhage due to tooth extraction is not a hazard in patients with hypertension However the possibility of an untoward cardiovascular reaction to the inadvertent intravascular injection of *anesthetic agents* which contain epinephrine must always be considered in patients with high blood pressure Furthermore nitrous oxide anesthesia may result in an acute rise in arterial blood pressure Many of the commonly used antihypertensive drugs potentiate the barbiturates *used for pre*operative or postoperative medication Furthermore hypotensive crisis may be precipitated during general anesthesia in patients taking rauwolfia preparations

Role of the cardiologist in dental management

As has been indicated briefly dental procedures *in patients with arteriosclerotic* heart disease present a small but definite risk On the other hand poor dental health may result in secondary systemic disease which may be fatal in the presence of the cardiac disease The situation is complicated by the fact that both dental and *cardiac diseases increase with age* Much of the difficulty could be avoided by early institution of dental care in cardiac patients The cardiologist must not assume that the patient is receiving adequate dental care When the cardiologist sees a patient with early arteriosclerotic hyper*tensive or valvular heart disease he recog*nizes the fact that despite his best efforts the disease will usually progress He must also recognize that existent dental disease will also progress Therefore he should take steps immediately to make sure that the patient s oral hygiene and dental health are in the best possible state at all times Necessary extractions periodontal therapy and replacement of lost tooth structures should be performed as soon as possible after the diagnosis of heart disease is established

The cardiologist should not rely on his own examination of the teeth to determine whether dental care is indicated Indeed periapical infection may be present in the absence of objective or subjective signs of *tooth infection If dental problems are* allowed to accumulate in patients with cardiac disease eventually the dentist or oral surgeon will be faced with a patient who is in need of extensive dental care but who has poor cardiac reserve Treatment of such poor risk patients is rarely *satisfactory* It is often necessary to make therapeutic compromises and in some instances the treatment of choice may be no treatment at all In addition whatever procedures are performed are undertaken at increased risk

The cardiologist should consider the fact *that with* the progression of cardiovascular disease the patient may become debilitated and bedridden or a cerebrovascular acci

dent may place him in a wheel chair. Under such circumstances it may be extremely difficult, if not practically impossible, to provide adequate dental care. Another reason for instituting early dental care in patients with cardiac disease is that at some time the patient may become obtunded or comatose secondary to myocardial infarction, cerebrovascular accident, or narcotics used in therapy. Foci of infection in the periodontal tissues may discharge purulent material which in turn may be aspirated into the lungs to produce pulmonary infections and decrease the chances of recovery from the primary disease.

The importance of early and complete dental care should be carefully explained to the patient. The patient should be adequately informed that the risk of dental procedures increases with time, whereas early therapy carries no risk. The patient should also be reminded of the fact that he is better prepared to finance dental care while he is working than after he has retired or has become too ill to work and his income has decreased. Furthermore, the total cost of dental care will most likely be greater if the teeth are neglected and the dental diseases allowed to become extensive.

If dental procedures do become necessary in patients with severe coronary arteriosclerosis and ischemic heart disease, certain precautions should be considered. It may be advisable to extract only one or two teeth at a time. However, the hazard of frequent dental manipulations of short duration should be weighed against the hazard of more prolonged manipulation with fewer visits. It must always be remembered that certain patients cannot tolerate prolonged dental therapy. The amount of dental manipulations which the patient with severe cardiac disease can safely tolerate should be decided by both the dentist and the physician in consultation. In patients with frequent episodes of angina pectoris, nitroglycerin should be placed under the tongue before pain develops. If a particularly difficult extraction is expected, mild sedation or a narcotic should be administered. As little epinephrine as necessary should be used in the local anesthesia. It has been recommended that no more than 10 c.c. of 1:50,000 epinephrine be used at any one time in persons with cardiac disease.[4] (This volume is rarely approached in current dental practice.) At all times the patient should be reassured and handled gingerly and patiently so as to allay fear and anxiety as much as possible. Dosages of cardiac drugs such as digitalis, quinidine, and procaine amide should be carefully regulated prior to dental therapy in order to avoid the side effects of these drugs during dental procedures. In patients receiving anticoagulants, prothrombin time should be allowed to decrease to the lower limits of the therapeutic range.

Hypertensive patients taking rauwolfia preparations should not be given a general anesthetic agent. After rauwolfia therapy is discontinued, it is necessary to wait at least 2 weeks before general anesthesia can be considered to be safe.

In patients with congenital and rheumatic heart disease the cardiologist should again be certain that the patient has the best possible oral hygiene. If tooth extraction becomes necessary in patients with congenital or rheumatic heart disease, parenteral penicillin should be administered at the time of the extraction and for a few days thereafter. If the patient is sensitive to penicillin, erythromycin should be employed. Oral penicillin should be used only when the complete cooperation of the patient is fully assured. In patients with rheumatic heart disease receiving prophylactic penicillin therapy, it is important to recognize the fact that the dosages of penicillin employed for prophylaxis against Group A beta hemolytic streptococci are inadequate to prevent bacterial endocarditis. Therefore, even in patients receiving prophylactic penicillin therapy, additional penicillin should be administered in preparation for dental procedures in order to insure high concentrations of penicillin in the blood.

The patient with congenital or rheumatic heart disease should be prepared for periodontal procedures and other procedures traumatic to the soft tissues in the same manner as for tooth extractions. Furthermore, the trauma associated with periodontal therapy should be kept to a minimum.

Physicians have always been interested in unusual oral manifestations of systemic disease However there has been a lack of interest in the ordinary problems of oral hygiene and continued dental care Most physicians perform only the most cursory examination of the teeth and medical schools provide no instruction to students concerning problems of oral hygiene and dental health The prevalent attitude of leaving the problem of oral hygiene to the patient may be detrimental to the patient s health and may ultimately result in an increase in the risk and extent of dental procedures The physician should obtain a dental consultation in the same manner and with the same exchange of information and thought as he does when he consults physicians in other specialties

Rapid advances in both medical and dental therapy have made communication between physicians and dentists in the form of joint conferences and the like not only highly desirable but necessary Because of the increased aging population of this country dentists and oral surgeons will treat an increasing number of patients with cardiovascular disease The cardiologist must be acquainted with the nature of the various dental procedures if he is to provide his patient with the best treatment and advice It is the cardiologist who is best able to evaluate the reserve of the cardiac patient and it is he who should advise the dentist of which procedures can be performed safely in a particular patient Unless the cardiologist has some knowledge of the various dental procedures he is in no position to evaluate the ability of the patient to tolerate dental therapy On the other hand the experiences of dentists and oral surgeons with cardiac patients should guide the cardiologist in determining whether a particular procedure is safe for his patient Unfortunately the cardiologist has little opportunity to learn of the experiences of dentists with cardiac patients Joint conferences between dentists and physician would help to provide the cardiologist with such information Because of mutual problems dentists may find it advisable to join the American Heart Association

Summary

Few people possess and maintain excellent oral hygiene at all times Thus it is to be expected that most patients with heart disease have unmet dental needs In such patients dental care should be obtained as early as possible The patient should not be permitted to wait until the cardiac disease has become so serious that dental procedures which would have been innocuous earlier have become hazardous The cardiologist should insist that the patient with heart disease maintain an excellent state of oral hygiene and dental health The cardiologist knows the natural history of cardiac disease He knows for example that a patient with coronary artery disease may develop a myocardial infarct at any time If good dental care is obtained before the development of the myocardial infarct continued maintenance of dental health should not be difficult However if dental problems are allowed to accumulate restoration of dental health may be impossible Most dental diseases are curable and should be attended to early when the cardiologist and dentist can elect the proper time and procedures rather than later when they are compelled to institute compromise therapy under adverse medical and dental circumstances and when the dental disease is irreversible

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The significance of the state of the central autonomic nervous system for quantitative and qualitative aspects of some cardiovascular reactions

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In an extensive series of experiments[7, 13, 14] the reactivity of the hypothalamus was altered directly by procedures such as electrocoagulation or intrahypothalamic injection of drugs or indirectly through reflexes, particularly those involving the sino-aortic baroreceptors. The aim of these investigations was twofold: to develop methods by which the state of activity of the autonomic nervous system at the level of the hypothalamus can be ascertained in the intact organism, and to devise physiologic procedures by which the reactivity of the hypothalamus can be altered. Since cardiovascular reactions served as tests in these studies, it may not be superfluous to review this material from a different point of view. An attempt is made, therefore, in this paper to review the role of the hypothalamus in some cardiovascular reactions and to suggest clinical implications of this work.

Methods

The investigations were performed on several hundred cats, mostly anesthetized with Pentothal and local anesthesia later supplemented by Intocostrin. Artificial respiration was used routinely. Hess electrodes served for stimulation of the hypothalamus. For the injection of 0.04 c.c. or less of procaine (1 per cent), Pentothal (4 per cent), strychnine (1 per cent), and Metrazol (10 per cent) into this structure a 28 gauge needle inserted between the stimulating electrodes was used. The blood pressure and contractions of the nictitating membranes (n.m.) were recorded by means of Statham pressure transducers and Statham dynamometers with a Brush amplifier and oscillograph. The pulse rate was recorded with an ordinate writer, an increase in the vertical stroke indicated a decrease in the pulse frequency. The hypothalamus was stimulated by means of a square wave generator. Small lesions surrounding the uninsulated tips of the Hess electrodes inserted into the hypothalamus were produced by passing the current from a high frequency generator through the Hess electrodes to an earth located in the head holder. This current (2 Mc/s frequency, 30 Ma for 15 seconds) produced a 1 to 2 mm. lesion without stimulating the cat. Larger lesions were sometimes produced by raising the tips of the electrodes 2 mm. The brains were fixed in 10 per cent formaldehyde, embedded in paraffin, and

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the cells stained with cresyl violet Cells whose nuclei failed to stain were considered to be destroyed

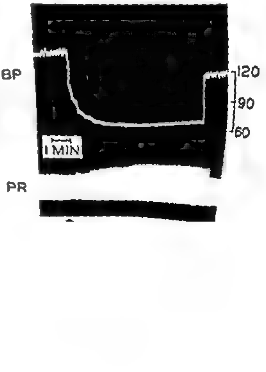
I Hypothalamically induced changes in cardiovascular reactions

Although phasic reactions of blood pressure and heart rate are easily elicited from various parts of the brain stem including the hypothalamus the tonic influence of the latter on cardiovascular functions was not established until recently In order to demonstrate the role of the hypothalamus on the resting level of blood pressure and heart rate it is necessary to avoid the surgical sectioning of the brain stem with its irritating effects Instead drugs were injected intrahypothalamically in minute amounts or lesions were produced through high frequency currents in circumscribed parts of the hypothalamus Since earlier work indicated that the anterior division of the hypothalamus mediates chiefly parasympathetic functions whereas the posterior division elicits sympathetic effects the action of the above named procedures on blood pressure and pulse rate must be considered separately for the two main hypothalamic divisions

Tonic cardiovascular functions of the posterior hypothalamus If a small amount of Pentothal is injected into the posterior division of the hypothalamus blood pressure and heart rate begin to fall immediately (Fig 1) Both recover to approximately the preinjection level after 20 to 40 minutes Such effects are obtained best on bilateral injection regardless of whether Pentothal Nembutal or procaine is used In 16 experiments the average fall in the blood pressure was 49 mm Hg the minimum and maximum were 10 and 80 mm Hg respectively The heart rate fell in 11 of 14 experiments in 3 experiments the pulse rate rose and the blood pressure decreased The site of injection was in most instances in the posterior hypothalamus close to the mammillary bodies and also in the infundibulum [27]

Similar results were obtained in 18 experiments in which discrete lesions were produced in the posterior hypothalamus unilaterally and bilaterally through high frequency currents The fall in blood pressure was somewhat smaller but the decrease in heart rate was more regular than in the injection experiments In no instance did the pulse rate rise and in only one experiment was it unchanged By passing the high frequency current through each of three Hess electrodes (separated by a distance of 1 5 mm) on each side and recording blood pressure and heart rate at the same time it was seen that with progressing coagulation i e with increasing size of the lesion the hypotensive and pulse rate slowing effect increased These effects were only partially reversible in the acute experiment [18]

The simultaneous decrease in blood pressure and heart rate as the result of a lessened activity of the posterior hypothalamus after electrocoagulation or intrahypothalamic injection of barbiturates seems to indicate that tonic impulses are transmitted from the hypothalamus to the medullary vasomotor and cardioaccelerator centers The increased pulse rate which accompanied the fall in blood pressure in 3 drug experiments appears to be due to baroreceptor reflexes which as we shall see later are weakened but not abolished by hypothalamic lesions



If minute amounts of strychnine or Metrazol are injected into the posterior hypothalamus, blood pressure and heart rate increase. These effects are opposite to those which result in a lessened hypothalamic activity after coagulation or injection of Pentothal into the sympathetic division of the hypothalamus. They are similar, however, to the changes produced by a mild electrical stimulation of the posterior hypothalamus. It is concluded, therefore, that with increased activity of the posterior hypothalamus increased sympathetic hypothalamic discharges are transmitted to the medulla oblongata.

Tonic cardiovascular functions of the anterior hypothalamus. Injection of barbiturates into the anterior hypothalamus showed that the partial elimination of this structure tends to increase pulse rate and blood pressure.[23] This tendency appeared to an even greater extent in 10 experiments in which lesions in the anterior hypothalamus were produced by electrocoagulation.[16] The rise in blood pressure was insignificant in 3 experiments and averaged 21 mm. Hg in the other 7 experiments. The heart rate increased in 7 of the 10 experiments with an average of 26 per minute. The effect of lesions in the anterior hypothalamus is in general less than that produced by lesions in the posterior hypothalamus. These experiments suggest a tonic activity of the anterior hypothalamus, the reduction of which leads to an increase in blood pressure and heart rate.

The anterior lesions destroyed mainly the following nuclei: preopticus, supraopticus, suprachiasmaticus, hypothalamicus anterior, whereas the posterior lesions involved chiefly the nuclei mammillaris ventrolateralis, lateralis, and posterior.

Influence of changes in the excitability of the posterior hypothalamus on phasic cardiovascular reactions. The procedures which were used for the study of the influence of the hypothalamus on tonic cardiovascular functions served likewise for an investigation of baroreceptor reflexes. The question investigated was whether and how

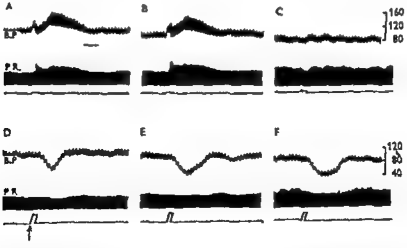


Fig. 2. The effect of unilateral coagulation of the posterior hypothalamus (between *A* and *B* and *D* and *E*) and bilateral coagulation of the posterior hypothalamus (between *B* and *C* and *E* and *F*) on the excitability of the posterior hypothalamus and the action of acetylcholine. Note that with progressive coagulation the hypothalamic response to electrical stimulation progressively diminishes, whereas the hypotensive effect of acetylcholine increases.[7] *A*, Left posterior hypothalamic stimulation (square wave currents 1.0 V, 99 pps, 0.8 ms, 4 sec.), control. *B*, Same as *A* after right posterior hypothalamic coagulation. *C*, Same as *A* after left posterior hypothalamic coagulation. *D*, 5 gammas of acetylcholine, control. *E*, 5 gammas of acetylcholine after right posterior hypothalamic coagulation. *F*, 5 gammas of acetylcholine after left posterior hypothalamic coagulation. Horizontal bar in *A* = 10 second. (From *Autonomic Imbalance and the Hypothalamus: Implications for Physiology, Medicine, Psychology and Neuropsychiatry*.[7])

these reflexes were altered when the excitability of the hypothalamus was changed either by the intrahypothalamic injection of drugs or through hypothalamic lesions.

It is well known that a rise in blood pressure (and therefore in sino-aortic pressure) intensifies the baroreceptor discharges and leads to a slowing of the heart rate, whereas a fall in pressure releases the sympathetic autonomic centers from the restraining action of the baroreceptors. The increased sympathetic or sympathetico-adrenal activity is indicated by an increased heart rate, a quick restitution of the blood pressure, and a contraction of the sympathetically innervated nictitating membranes (n.m.). These effects are easily studied with hypertensive and hypotensive drugs, respectively.[4,9,10,11]

Increasing the excitability of the posterior hypothalamus by the injection of strychnine into this structure changed considerably the action of hypotensive drugs such as acetylcholine, Mecholyl, and histamine. The rise in blood pressure after the hypotensive phase was faster and the reduction in pulse pressure during the fall of the blood pressure was less than in the control test. Moreover, the acceleration of the heart rate was increased and prolonged. These changes associated with a greatly augmented contraction of the sympathetically innervated n.m. support the interpretation that the reflexly activated sympathetic system is more responsive to the fall in blood pressure induced by acetylcholine after the excitability of the posterior hypothalamus had been raised than under control conditions. Similar results were obtained with Mecholyl and histamine. The latter drug has the tendency to cause a marked overshooting of the blood pressure after the hypotensive phase under conditions of raised excitability of the posterior hypothalamus, and this overshooting is absent or of much lesser degree in the control test. Here again the hypertensive phase is associated with an increased acceleration of heart rate and increased contraction of the n.m. Even unilateral injection of strychnine or Metrazol into the hypothalamus is effective in this respect.[7,11]

Instead of using the intrahypothalamic injections of drugs, the excitability of the sympathetic division of the hypothalamus can also be raised by a mild electrical stimulus applied either unipolarly or bipolarly through the Hess electrodes. Such procedures likewise increase the sympathetic reflexes elicited by the hypotensive action of acetylcholine, Mecholyl, and histamine. This increased responsiveness appears again as a quicker return of the blood pressure from the hypotensive phase, an overshooting of the blood pressure, increased acceleration of the heart rate, and augmented contraction of the n.m.[6]

It is of interest to point out that even the subthreshold stimulation of the posterior hypothalamus with square wave currents or condenser discharges which change neither the blood pressure nor the heart rate alters the action of hypotensive drugs in the manner we have just described. Similarly, it was found that the intrahypothalamic injection of strychnine or Metrazol is effective in altering the responsiveness of the cardiovascular system to hypotensive drugs even in those cases in which the intrahypothalamic injections failed to alter blood pressure and heart rate or in which this effect had disappeared when the hypotensive test drug was applied.

In another group of experiments the influence of a reduction in sympathetic hypothalamic reactivity on the action of hypotensive drugs was investigated. The reduction in hypothalamic reactivity was accomplished by intrahypothalamic injection of Pentothal or procaine or by electrocoagulation of a part of the posterior hypothalamus.[16,17] The results are illustrated by Fig. 2 which shows the action of acetylcholine before and after coagulation of the posterior hypothalamus. It is noted that with progressive coagulation the hypotensive action of acetylcholine increases and the sympathetic responsiveness of the hypothalamus to direct stimulation declines. Similar results were obtained when Mecholyl or histamine w... used. It was also noted that when th... hypotensive drugs elicited a contract... the n.m. under control conditi... contraction was greatly reduced ... ished when the test was repeated ... excitability of the posterior h... had been diminished by ... trahypothalamic injection...

It is inferred from these experiments that the state of excitability of the sympathetic division of the posterior hypothalamus has a decisive influence on the action of hypotensive drugs. If the excitability of the posterior hypothalamus is diminished, the recovery from the hypotension is delayed and/or less complete than under control conditions. If the excitability is increased, the return of the blood pressure to the control level is accelerated and the tendency to a secondary hypertensive phase is enhanced. The changes in heart rate and the contraction of the n.m. show that hypotensive drugs elicit sympathetic reactions the intensity of which parallels the excitability of the posterior hypothalamus.

Anterior hypothalamus and phasic cardiovascular reactions. For a test of parasympathetic cardiovascular reactions in relation to the excitability of the anterior hypothalamus, noradrenaline-induced slowing of the heart rate was used.

Two groups of experiments were performed. In one group the excitability of the anterior hypothalamus was reduced by the intrahypothalamic injection of Pentothal or Nembutal[9]; in the other, lesions were produced in the anterior hypothalamus by high-frequency currents.[illegible] The results were similar in both groups and showed that the noradrenaline-induced slowing was lessened when the excitability of the anterior hypothalamus was decreased. In the experiments involving the intrahypothalamic injection of barbiturates it could be shown that this effect was reversible.

It is of interest to point out that not infrequently the pressor effect of noradrenaline was increased after the excitability of the anterior hypothalamus had been diminished. As Fig. 3 shows, even under these conditions the slowing of the heart rate was less than in the preceding control test. If one bears in mind that, other conditions being equal, the noradrenaline-induced slowing increases with increasing pressor effect, the experiment of Fig. 3 is a proof *a fortiori* for the statement that a reduction in the excitability of the anterior hypothalamus is associated with a diminution in the noradrenaline-induced slowing of the heart rate.

Some observations on the influence of the hypothalamus on respiration. It is known from several investigations, particularly that of Hess,[illegible] that stimulation of the diencephalon frequently causes parallel respiratory and cardiovascular changes. The posterior hypothalamus in particular leads to responses of increased blood pressure and an increase in the frequency of respiration, whereas the anterior hypothalamus and adjacent areas cause mainly a fall in blood pressure and a diminution in respiration. In view of the fact that lesions of or injection of barbiturates into the posterior hypothalamus disclosed the existence of tonic sympathetic discharges from the hypothalamus which contribute to the maintenance of blood pressure and heart rate, the question was investigated whether a similar tonic influence exists with respect to respiration. Experiments in which the excitability of the posterior and lateral hypothalamus was reduced through high-frequency lesions or intrahypothalamic injection of drugs in noncurarized cats showed that parallel with the fall in blood pressure and a decrease in heart rate, the respiratory movements declined in frequency.[illegible] The ergotropic zone (Hess) of the hypothalamus seems to supply tonic impulses to respiratory and vasomotor centers.

II. Tuning of the autonomic system through baroreceptor reflexes

The experiments described in the preceding sections showed the influence of changes in the state of excitability of the hypothalamus on certain vascular reactions involving sino-aortic baroreceptor reflexes. They suggest that it may be possible to alter autonomic balance and reactivity to hypothalamic stimuli through these reflexes.

For the sake of simplicity of description the following terminology is adopted. Since the fall in blood pressure (and consequently in sino-aortic pressure) diminishes the intensity of the parasympathetic baroreceptor discharges and releases sympathetic centers, it is said to induce a state of sympathetic tuning. Conversely, a state of parasympathetic tuning is said to prevail if the activity of the baroreceptors is increased through a rise in intrasinusal pressure. Therefore, what is to be

investigated is the state of the hypothalamus in these reflexly induced states of autonomic tuning.[7,13]

Numerous experiments showed that stimulation of the sympathetic division of the hypothalamus becomes much more effective in the state of sympathetic tuning induced by the injection of hypotensive drugs than in control conditions. The stimulus is applied during the hypotensive phase as the blood pressure begins to recover. The increased sympathetic responsiveness is evident from the greater rapidity of the contraction of the n.m. and its magnitude, the quicker and more complete recovery of the blood pressure from the hypotensive phase, and the greater acceleration of the heart rate. Depending on the parameters of the hypothalamic test stimulus, any or all indicators are positive and in most instances the effect of tuning is very large. Near threshold hypothalamic stimuli which are without effect on the n.m. and heart rate in the control test may cause a marked response of these indicators during sympathetic tuning. If contractions of the normal and the denervated n.m. are recorded (the latter serving as an indicator of adrenomedullary secretion), it is seen that a hypothalamic stimulus which under control conditions evokes a contraction of the normal but not of the denervated n.m. elicits also a response of the latter in the state of sympathetic tuning. Since a transition from a sympathetic to a sympathetico-adrenal response occurs when the degree of sympathetic stimulation[1] or the state of excitability is increased, this qualitative change in the autonomic reactivity likewise testifies for the increased sympathetic reactivity in sympathetic tuning. It should be added that these effects are reversible and occur regardless of whether the fall in sino-aortic pressure is induced by drugs (acetylcholine, Mecholyl, histamine) or results from bleeding,[14] or the application of low frequency stimuli to the central end of the sciatic nerve.[1]

If, on the other hand, the intrasinusal pressure is increased through noradrenaline or adrenaline, or if the test stimulus is applied during the hypertensive phase which frequently follows the histamine-induced hypotension, it is found that these states of reflexly induced parasympathetic tuning are characterized by increased responsiveness of the parasympathetic system. The test stimuli consist of stimulation of either the hypothalamus or the afferent fibers in the sciatic nerve. In each case low frequency stimuli (about 3 to 10 per second) are applied which, under control conditions, produce a slight fall in blood pressure and heart rate. These effects are distinctly augmented during the state of parasympathetic tuning; a greater deceleration of the heart rate occurs although the rise in blood pressure during the interaction of noradrenaline and the parasympathetically acting stimulus is, of course, somewhat less than that seen in the control test when noradrenaline is administered by itself.

These experiments were performed also after sino-aortic denervation.[9] Changes in blood pressure, whether due to bleeding

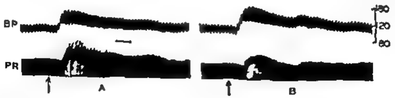


Fig. 3. The effect of bilateral injection of Pentothal into the anterior hypothalamus on noradrenaline-induced reflex slowing (injections indicated by arrows). Note that the reflex slowing of the heart rate is lessened after the injection of Pentothal in spite of the greater rise in the blood pressure. *A*, 2.5 gammas of noradrenaline intravenously. *B*, 2.5 gammas of noradrenaline intravenously after bilateral injection of 0.04 c.c. of Pentothal (40 mg./c.c.) into the anterior hypothalamus. (From *Autonomic Imbalance and the Hypothalamus. Implications for Physiology, Medicine, Psychology, and Neuropsychiatry*.[7])

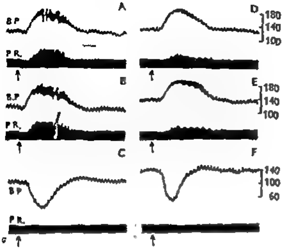


Fig. 4. The effect of bilateral anterior hypothalamic coagulation on the reflex slowing induced by noradrenaline and on the hypotensive action of acetylcholine. Note that the noradrenaline-induced reflex slowing is diminished and that the recovery of the blood pressure from the acetylcholine-induced hypotension is accelerated.[7] *A*, 7.5 gammas of noradrenaline (control). *B*, 10 gammas of noradrenaline (control). *C*, 5 gamma of acetylcholine (control). *D*, 7.5 gammas of noradrenaline after bilateral anterior hypothalamic coagulation. *E*, 10 gammas of noradrenaline after bilateral anterior hypothalamic coagulation. *F*, 5 gammas of acetylcholine after bilateral anterior hypothalamic coagulation. (From *Autonomic Imbalance and the Hypothalamus: Implications for Physiology, Medicine, Psychology, and Neuropsychiatry*.[7])

reinjection of blood or drugs no longer had any effect on the reactivity of the autonomic nervous system. It is concluded, therefore, that the alteration in autonomic reactivity described in this section is the result of an alteration in the intensity of baroreceptor reflexes.

Hypothalamic reciprocal relations. It was mentioned earlier that the reduction in the excitability of the anterior hypothalamus tended to increase the blood pressure and heart rate, whereas the opposite effect prevailed when the excitability of the posterior hypothalamus was lessened. These observations suggest a reciprocal relation between the two divisions of the hypothalamus in so far as cardiovascular reactions are concerned. Appropriate experiments showed indeed that when the excitability of the anterior hypothalamus was diminished that of the posterior hypothalamus was increased. This was indicated by an augmentation of the sympathetic effects of a standard stimulus applied to the posterior hypothalamus; the effect on the blood pressure and n.m. was greater than under control conditions.

If the posterior hypothalamus is released as the result of the injection of barbiturates into the anterior hypothalamus or after the electrocoagulation of a part of this structure, one would expect that certain cardiovascular reactions would be altered as in experiments in which the excitability of the posterior hypothalamus had been increased. (In the latter condition the hypotensive action of acetylcholine, histamine, etc., was lessened, the tendency to a hypertensive phase was increased, and the acceleration of the heart rate was greater than under control conditions.) The experiments validated this expectation and showed that regardless of whether the excitability of the posterior hypothalamus was released (through reduction in the activity of the anterior hypothalamus) or increased through direct electrical stimulation or through the injection of drugs such as strychnine or Metrazol (applied to the posterior hypothalamus), similar changes occurred in the action of hypotensive drugs.

The reciprocal behavior of parasympathetic and sympathetic reflexes after the electrocoagulation of the anterior hypothalamus is illustrated in Fig. 4. Whereas this procedure leads to a diminution of the parasympathetic reflex—the slowing of the heart rate is less in *D* and *E* than in *A* and *B* in spite of similar rises in the blood pressure, the sympathetic reflex reactivity is increased: acetylcholine leads to a quicker return of the blood pressure and a more distinct acceleration of the heart rate in *F* than is seen in the control test *C*.

Further studies showed that coagulation of the posterior hypothalamus leads to a release of the anterior hypothalamus: its excitability is increased, as indicated by the fact that in response to a given rise in blood pressure the slowing of the heart rate is greater after coagulation than in the control test.[18]

It is concluded that the law of reciprocal relations is valid for the autonomic system at the hypothalamic level. It is demonstrable in states of autonomic imbalance

produced by lesions in either the parasympathetic or the sympathetic division of the hypothalamus. The changes in autonomic reactivity are apparent not only from the effect of stimuli acting directly on the hypothalamus but also from the action on blood pressure and heart rate of noradrenaline and acetylcholine which elicit via the baroreceptors autonomic reflexes the intensity of which, other conditions being equal, is determined by the excitability of the respective division of the hypothalamus.

Reciprocal changes in reflexly induced states of autonomic tuning. Our next task is to describe the changes in the reactivity of the sympathetic system during parasympathetic tuning and vice versa. For this purpose a series of experiments was performed in which during the noradrenaline induced tuning the sympathetic division of the hypothalamus was stimulated and the effect was compared with that seen under control conditions before and after tuning. The results were uniform and showed a marked reduction in sympathetic responsiveness indicated by a lessened contraction of the n.m. and a diminution in or absence of the rise in blood pressure and heart rate. These results were obtained regardless of whether the tuning was due to a rise in intrasinusal pressure resulting from the injection of noradrenaline or adrenaline. Similar effects were recorded during the hypertensive phase which followed the fall in blood pressure after histamine.[7] Moreover, a hypothalamic stimulus which elicited marked sympathetic responses on ocular and vascular indicators after moderate bleeding elicited only minimal changes in n.m. and blood pressure after the blood had been reinjected.

In order to test the parasympathetic reactivity during the state of sympathetic tuning experiments with hypotensive drugs are not feasible since in the hypotonic condition the noradrenaline induced slowing of the heart rate fails to appear. It is necessary, therefore, to produce sympathetic tuning by other means. For this purpose a near threshold stimulus was applied either to the sympathetic division of the hypothalamus or to the central end of the sciatic nerve. Stimuli which caused only minimal or no changes in blood pressure and heart rate lessened distinctly the pulse slowing action of noradrenaline when the latter was administered during the sympathetically induced state of tuning. This result occurred although the interaction between the sympathetic excitation and the noradrenaline on the blood pressure resulted in a slightly higher blood pressure than in the control test in which noradrenaline was injected by itself. Since in spite of these factors favoring a greater pulse slowing, this response was actually decreased, it may be concluded that sympathetic tuning causes a reduction in parasympathetic reactivity. Other parasympathetic reactions (see Reference 7) were likewise diminished in this condition.

Bearing in mind the previously discussed experiments which showed an increased sympathetic responsiveness in the state of sympathetic tuning and an increased parasympathetic responsiveness in the state of parasympathetic tuning, one may say that the reciprocal relations which characterize the action of the baroreceptors on autonomic centers[6] persist in these states of reflexly induced tuning. The reciprocity of these actions tends to further increase the state of autonomic imbalance which results from a fall or rise in the blood pressure.

State of tuning and the reversal of autonomic reactions. It is frequently seen that

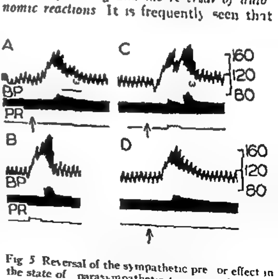


Fig. 5. Reversal of the sympathetic pressor effect in the state of parasympathetic tuning induced by noradrenaline. Chloralose anesthesia. A and D: 0.0008 mg./kg. of noradrenaline intravenously at the arrow. C: This injection is followed by stimulation of the left posterior hypothalamus (1 V, 179/sec, 0.8 ms, for 8 sec.). B: Stimulation of the hypothalamus (as in C) alone. (By permission of Springer Verlag, Vienna.)

in the state of parasympathetic tuning induced by noradrenaline or other procedures even more dramatic changes in the reactivity to sympathetic stimuli occur: instead of eliciting a lesser sympathetic response a reversal occurs.[7,8] The sympathetic stimuli elicit a parasympathetic-like effect. Fig. 5 shows an experiment in which noradrenaline by itself causes a moderate slowing of the pulse (*A*, *D*), whereas the hypothalamic stimulus produces a very large rise in blood pressure and a slight acceleration of the heart rate (*B*). This stimulus is applied in Fig. 5 *C* during the noradrenaline-induced hypertensive phase at the moment at which the reflex slowing appeared. During the first 2 to 3 seconds the blood pressure continued to rise slightly and then fell by about 20 mm. Hg during the remainder of the stimulation period. Hereafter the blood pressure rose, while the post-stimulatory parasympathetic induction appeared in the record of the heart rate.*

This reversal may likewise occur in the heart rate, so that a fall in blood pressure and heart rate was recorded in the state of parasympathetic tuning in response to a stimulus which evoked marked sympathetic effects in all indicators. Moreover, the reversal is not specific for the noradrenaline-induced state of tuning but was seen in various forms of parasympathetic tuning. It was induced not only by noradrenaline and adrenaline but appeared also during the hypertensive phase of histamine and that produced by hypothalamic stimulation, provided that the pressor effect was very large.†

Finally, Fig. 6 illustrates that such a reversal may occur on reinjection of blood after previous bleeding or on injection of dextran.[14] The figure shows that, whereas the hypothalamic stimulus evokes a pressor effect under control conditions (*A*), a fall in blood pressure and heart rate is seen after dextran (*B*). This reversal is associated with a reduction in the contraction of the n.m., an effect which is typical for the reactivity of the sympathetic system in states of parasympathetic tuning.

*Slowing of the pulse after the cessation of the sympathetic hypothalamic stimulus is a rebound phenomenon which has been analyzed elsewhere.[8]

†The reason for the quantitative differences will be discussed later.

Discussion

In spite of the startling effects on blood pressure and heart rate (and also on respiration) which result from lesions and other procedures that alter the excitability of the hypothalamus, it should be stressed that the main regulatory center of these cardiovascular functions is the medulla oblongata, as Wang[2] in confirmation and extension of earlier work has shown. The tonic effects of the hypothalamus appear only if the anesthesia is very light and the irritating effect of surgical lesions used in earlier work[1] is eliminated. Electrocoagulation and injection of minute amounts of drugs cause similar effects under these conditions, but their action depends on the hypothalamic site. A fall in blood pressure and heart rate results from a lesion or reduction in excitability of the posterior hypothalamus, indicating that this part exerts a tonic influence on the sympathetic medullary centers. On the other hand, the anterior hypothalamus seems to send tonic impulses to the parasympathetic medullary centers, which is apparent from the rise in blood pressure and heart rate after anterior hypothalamic lesions are produced, but the influence of the anterior hypothalamus is less than that of the sympathetic division of the hypothalamus. Since the sino-aortic reflexes persist in decerebrate animals, it is understandable that even extensive hypothalamic lesions do not lead to a permanent fall in blood pressure in all animals.[1] The reactivity of the sympathetic system after the production of anterior hypothalamic lesions suggests a release of hypothalamic sympathetic centers with subsequent increase in impulse traffic to the sympathetic medullary centers and further a diminution in activity of the medullary vagal centers due to lessened transmission from the anterior hypothalamus. Conversely, the greater reactivity of the parasympathetic system after posterior hypothalamic lesions are produced seems to be caused by a release of the vagal center and to involve corresponding mechanisms.

One of the major results of the present work is the fact that alterations in autonomic excitability and balance of the hypothalamus are reflected in responsiveness of it not only to direct stimulation but in its reaction to reflex stimuli. Detailed

investigations showed in particular that the baroreceptor reflexes are quantitatively altered under these conditions. In view of the long-established modulation of autonomic functions from the cortical, especially limbic,[8] and hypothalamic levels,[6,7] these results were to be expected. They are, however, of considerable practical interest inasmuch as they suggest that different emotional states known to alter the excitability of the hypothalamic system may be related to different responses to Mecholyl and noradrenaline which can be used for the quantitative evaluation of baroreceptor reflexes in the intact organism. The observation that "anger in" is associated with an intensified hypotensive action of Mecholyl (prolonged hypotension and/or incomplete recovery) and that "anger out," on the contrary, is associated with a brief and mild hypotensive action of this drug[5] suggests, *in the light of our experiments*, that different central autonomic states prevail in these emotional conditions. "Anger out" is characterized by a higher degree of sympathetic excitability of the hypothalamic system than "anger in."[*] The fact that persons with aggressive tendencies in life situations ("anger out") show a greater g tolerance than do those reacting with anxiety ("anger in") in similar conditions[4] is in agreement with this *interpretation*.†

Even in the absence of emotional or environmental stress, *differences in the degree of tonic activity of the parasympathetic and sympathetic divisions of the hypothalamus* are highly probable in different persons. This assumption is supported by the finding of wide variations in sympathetic and parasympathetic reactivity (as disclosed by the Mecholyl and noradrenaline tests) in normal persons and psychiatric patients.[25] These variations are present at all ages although increasing age reduces sympathetic and parasympathetic responsiveness considerably. Deviation in *autonomic reactivity* and states of imbalance at the hypothalamic level seem to underlie *numerous clinical conditions* such as cerebral vascular attacks, vagotonia, etc. The work of Losse and associates[27] suggests on the basis of various circulatory and blood tests that in a small percentage of normal persons (8 per cent) the parasympathetic reactivity predominates and in a group of similar size the sympathetic reactivity. These groups represent the sympathotonics and vagotonics in contrast to the majority of normal persons (about 84 per cent) who belong to an autonomically mixed group without specific dominance of either autonomic reactivity. Since the autonomic reactivity of identical but not of fraternal twins is the same,[27] it is probable that the autonomic balance in the hypothalamus is determined by genetic factors. It is further assumed that under the influence of various stimuli (including the emotions) the imbalance is aggravated because repeated stimuli tend to have increasing effects on sympathetic centers including the hypothalamus (summation). Thus a stimulus which evokes a mild sympathetic effect (*rise in blood pressure* and heart rate and contraction of the n. m.) followed by a *post stimulatory "rebound"* (*reduced heart rate*) may, on repetition, *elicit sympathetic* responses of increasing intensity with disappearance of the para-

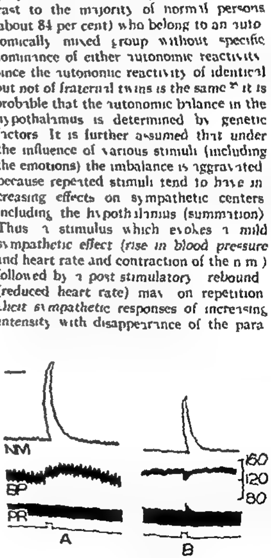


Fig. 6. Influence of dextran on the reactivity of the sympathetic division of the hypothalamus. *A* and *B*, Stimulation of the posterior hypothalamus with 3 V, 180/sec., 4 ms for 3.5 sec. Between *A* and *B* 20 c.c. of dextran was injected intravenously in a 3 kilogram cat.[1] (By permission of Springer Verlag, Vienna.)

*It is not assumed that the processes leading to different emotions are located in the hypothalamus but that they involve the brain stem, neocortex, and particularly the limbic cortex. Since, however, data showed the hypothalamus is the "nodal point" of this complex anatomic and functional system, it may be influenced in a specific manner regardless of whether the hypothalamic autonomic balance is altered directly via reflexes or through impulses reaching it from the neocortex or the limbic brain.

†For further discussion see References 7 and 15.

sympathetic rebound effects.[10] The mechanisms of summation and reciprocal inhibition which underlie these changes may well account for the development of pathologic phenomena associated with marked shifts in central autonomic imbalance.*

For an understanding of the physiologic and clinical implications of a shift in the autonomic hypothalamic imbalance it is important to emphasize that the hypothalamus has not only a profound influence on autonomic (and somatic) reactivity but also on the state of the cerebral cortex. If the state of excitation of the sympathetic division is increased, hypothalamic-cortical discharges are augmented and the state of awareness is enhanced while the cortical potentials show desynchronization.[7,15] Conversely, a reduction in the hypothalamic sympathetic reactivity lessens these discharges and leads to sleep (cortical synchrony). These effects can be produced experimentally not only through direct changes in the hypothalamus but also indirectly through baroreceptor reflexes. The effects of the latter are abolished by sino-aortic denervations.[13] The validity of these mechanisms for man is apparent from the fact that the lowering of the blood pressure through Mecholyl leads to psychomotor excitation, whereas the raising of the pressure through noradrenaline has the opposite effect and even frequently induces sleep.[1] Apparently, the significance of the baroreceptor reflexes is not confined to the circulatory system. On the contrary, they represent a mechanism whereby, through changes in the state of the hypothalamus and the hypothalamic-cortical discharges dependent on it, the state of the whole organism is altered.

Our experimental material seems to be of interest with respect to Wilder's "law of initial value."[20] This author has collected an impressive material which seems to show that certain autonomic reactions, such as that of the blood pressure to the injection of adrenaline, is determined by the initial level of blood pressure. Although it is correct to say that with extreme variations in blood pressure the effect of this drug on the blood pressure is inversely related to the initial value of the blood pressure, it is easy to demonstrate that *the central reactivity of the autonomic nervous system is determined by the nature and intensity of the antecedent stimuli and not simply by certain initial states such as that of the blood pressure.* For instance, if the blood pressure is raised from 100 to 130 mm. Hg by the injection of noradrenaline or adrenaline, *sympathetic reactivity is diminished.* If, however, a similar elevation in blood pressure is induced by stimulation of the central end of the sciatic nerve or of the sympathetic division of the hypothalamus, *sympathetic reactivity is increased.* The former represents states of parasympathetic tuning in our terminology, and the latter represents states of sympathetic tuning. In spite of identical levels of the blood pressure, the responsiveness of blood pressure, heart rate, and nictitating membranes to stimulation of the posterior hypothalamus is fundamentally different in the two states. Moreover, even qualitatively different responses may occur, as indicated by the reversal of the response of blood pressure to a sympathetically acting stimulus in states of parasympathetic tuning induced by the injection of drugs which raise the blood pressure, the injection of dextran, or the reinjection of blood after bleeding.

It is pertinent to mention that the state of tuning may be altered without change in blood pressure. If Wilder's "law" were valid, one would expect no change in autonomic responsiveness and certainly no change in the response of the blood pressure under such conditions. It is easily shown, however, that subthreshold stimuli applied to the central end of the sciatic nerve or the posterior hypothalamus increase the sympathetic responsiveness of the hypothalamus to a suitable test stimulus.

The reactivity of the autonomic centers in these and similar states of tuning are understandable if we take into consideration the fact that the "tuning" stimuli which impinge on a certain autonomic center cause processes of summation and potentiation with the test stimuli and, secondly, that reciprocal relations prevail in these states between sympathetic and parasympathetic centers. The summation and potentiation phenomena are illustrated by the following data.[19]

*For further discussion, see References 7, 10, 12, and 15.

1 The effectiveness of a stimulus acting directly or reflexly on a sympathetic center such as the posterior hypothalamus is greatly increased if it is applied during or shortly after another stimulus which likewise impinges on sympathetic centers Thus two hypothalamic stimuli acting on different sites two stimuli affecting the left and right sciatic nerves respectively and a combination of sciatic and hypothalamic stimuli* of suprathreshold and subthreshold intensity applied simultaneously or successively may be used to illustrate spatial and temporal summations Under these conditions a stimulus becomes more effective than in the control test (i e in the absence of the other stimulus) and its action is greater than that which corresponds to the algebraic summation of the two stimuli involved

2 Similar summation processes occur in the parasympathetic system They may result from the interaction of low frequency stimulation of two sciatic nerves or two hypothalamic sites or a combination of hypothalamic and sciatic stimulation [10]

3 The phenomena described under the term of reflex tuning are likewise explainable on the basis of summation processes If a state of parasympathetic tuning is produced by the injection of noradrenaline the parasympathetic discharge which impinges on the autonomic centers is increased and makes a parasympathetically acting test stimulus more effective than under control conditions A corresponding summation process accounts for the increased effectiveness of sympathetic stimuli in the state of sympathetic tuning

It was shown that reciprocal relations characterize the state of tuning elicited by centrally induced autonomic imbalances (coagulation of the sympathetic or parasympathetic division of the hypothalamus and related procedures) as well as by alterations in the baroreceptor reflexes (injection of hypotonic and hypertonic drugs) The inhibition of the parasympathetic system in states of sympathetic tuning and vice versa accounts for the fact that sympathetic reactivity is lessened in parasympathetic tuning and that parasympathetic reactivity is diminished in sympathetic tuning In addition these inhibitory actions are causally related to the following two phenomena

1 A rise in blood pressure which results from stimulation of the hypothalamus or the medulla oblongata or which is due to excitation of nociceptive nerves is accompanied in the experimental animal by an increase in heart rate Emotional excitement in man causes similar changes in blood pressure and pulse rate In neither case do baroreceptor reflexes become manifest As a matter of fact, a hypothalamic stimulus may raise the blood pressure by 80 or 100 mm Hg and greatly increase the heart rate whereas in the same animal a 40 mm rise in blood pressure induced by noradrenaline is accompanied by a marked fall in pulse rate The reason is that sympathetic excitation inhibits reciprocally the vagal center whereas the rise in blood pressure produced by noradrenaline increases the parasympathetic discharges from the baroreceptors which acting on the vagal center lead to a decrease in heart rate *

2 In states of parasympathetic tuning a reversal occurs a stimulus which elicits a rise in blood pressure in the control tests evokes a fall in pressure in the condition of parasympathetic tuning induced by the injection of noradrenaline Two factors are operative in this phenomenon First there is the greater responsiveness to parasympathetic stimuli and the reciprocal inhibition of the sympathetic centers Secondly it is assumed that a sympathetic stimulus while causing only overt sympathetic effects stimulates actually also parasympathetic neurons although to a much lesser extent This assumption is supported by the fact that a gradual shift from a parasympathetic to a sympathetic effect occurs as the frequency of stimulation is increased [18] If this is the case one must expect that in the state of parasympathetic tuning the sympathetic action is suppressed (by inhibition) and the parasympathetic is facilitated so that a reversal results

In the last analysis it is the balance between excitatory and inhibitory processes acting on a certain autonomic center which

Stimulati of th med lla bl gata may lso be ubst t ted for st mul t f th hypothal m s.

*The recip ocal I hibit f th sympath (vagal c) may

decides the effect This explains the fact that a fundamental change in autonomic reactivity may occur in conditions of very large rises in blood pressure which result from hypothalamic stimulation Whereas at moderately increased levels of blood pressure the sympathetic reactivity is increased a reversal of the blood pressure reaction in response to a sympathetically acting stimulus occurs at excessive levels of blood pressure Apparently the greatly increased discharges from the baroreceptors break through and create a condition of relative parasympathetic tuning (Fig 7)

Summary

Experimental studies are reported in which the influence of hypothalamic lesions and of states of altered hypothalamic excitability induced directly or via reflexes was investigated on autonomic and particularly cardiovascular reactions The chief results are as follows

1 Lesions in the posterior hypothalamus (sympathetic division) result in a fall in blood pressure and heart rate whereas lesions in the anterior hypothalamus (parasympathetic division) have the opposite effects Lesions in the posterior hypothalamus cause in addition a decrease in respiratory activity It is inferred that the hypothalamus sends tonic sympathetic and parasympathetic impulses to the medulla oblongata

2 Baroreceptor reflexes of sino aortic origin are modified by changes in the excitability of the hypothalamus and reflect thereby the state of central autonomic balance Hypotensive drugs (acetylcholine Mecholyl and histamine) cause a greater and more prolonged fall in blood pressure with lessened sympathetic reactivity of the posterior hypothalamus Conversely when the sympathetic reactivity of the hypothalamus is augmented the hypotensive action of the above named drugs is small a hypertensive phase follows the fall in blood pressure and the heart rate is accelerated Similarly the noradrenaline induced slowing of the heart rate parallels the degree of excitability of the anterior (parasympathetic) division of the hypothalamus

3 Baroreceptor reflexes influence the state of reactivity of the hypothalamus and

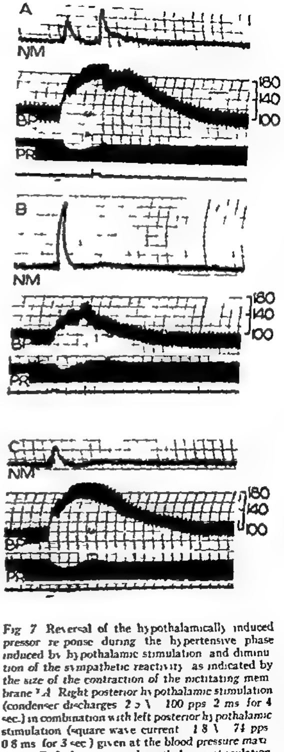


Fig 7 Reversal of the hypothalamically induced pressor response during the hypertensive phase induced by hypothalamic stimulation and diminution of the sympathetic reactivity as indicated by the size of the contraction of the nictitating membrane [1] *A* Right posterior hypothalamic stimulation (condenser discharges 2 5 V 100 pps 2 ms for 4 sec.) in combination with left posterior hypothalamic stimulation (square wave current 1 8 V 74 pps 0 8 ms for 3 sec) given at the blood pressure maximum *B* Left posterior hypothalamic stimulation as in *A* *C* Right posterior hypothalamic stimulation as in *A* (From *Autonomic Imbalance and the Hypothalamus Implications for Physiology Medicine Psychology and Neuropsychiatry* [7])

act not only on the autonomic system but also on the cerebral cortex through hypothalamic cortical discharges The rise in blood pressure (and thereby in intrasinusal pressure) on injection of noradrenaline causes an increased parasympathetic and diminished sympathetic reactivity of the hypothalamus and lessened cortical activity The fall in blood pressure after injection of acetylcholine etc causes an increased sympathetic and a decreased parasympathetic excitability of the hypothalamus and increased cortical activity These effects are abolished by sino aortic denervation

4 If the baroreceptor discharges are greatly increased autonomic reversal occurs Thus a stimulus which causes a sympathetic action under control conditions calls forth a fall in blood pressure when applied during the noradrenaline induced tuning of the autonomic system

5 In contradiction to Wilder s claims it is not the level of blood pressure by itself which determines the reactivity of the autonomic centers but the nature of the stimuli which act on them when the test stimulus is applied If the blood pressure is raised to the same degree by injection of noradrenaline and by hypothalamic stimulation (sympathetic division) the sympathetic reactivity is diminished in the former and increased in the latter case A general theory underlying the tuning of the autonomic system as manifested in cardiovascular reactions is presented

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Acute benign pericarditis

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The subject of this paper is misleadingly called benign since in some instances its complications are life threatening The term *pericarditis* is pathologically too limiting because in every recognized instance there is also myocardial involvement Therefore what is called *acute benign pericarditis* is more suitably termed *acute perimyocarditis*

The viral etiology of this illness probably will be more commonly recognized in the future with improvements in virologic technique A necessary complement to this is the early diagnosis by the physician and the realization that all severe precordial pain is not infarction This early suspicion is not only required for substantiating the clinical diagnosis but what is of greater importance it is vitally necessary in this era of anticoagulation

Incidence

If one excludes the pericarditis associated with infarction and uremic states the incidence of acute perimyocarditis in the general hospital population is low Its peak occurrence rates are during the fall and spring seasons and it is during these months that one may find a surge in incidence with the Coxsackie influenzal and other viral epidemics

There is no significant difference in sex incidence[1] Although the age groups of the third and fourth decades are most commonly affected it must be emphasized that this age incidence really should be ignored in the diagnosis of the individual patient Acute perimyocarditis does occur in the child as well as in the elderly adult

An awareness of current community epidemiological reports and an always searching type of history and physical examination will certainly afford a higher recognition rate than some reports of only 20 per cent accuracy in diagnosing pericarditis[2]

Signs and symptoms

Chest pain is the outstanding and most often the presenting complaint The onset is usually abrupt and if not at maximal intensity from the very beginning it soon reaches this level generally within 24 hours The pain is usually characterized as sharp or sticking The not too infrequent description of precordial distress which is squeezing dull or pressing prompts consideration of myocardial infarction Indeed the pain of pericarditis lends itself to many considerations by the diversity of its location and quality It may present as pain in both shoulders in the absence of chest pain and seems to be augmented by movements of the upper extremities Its location in the epigastrium or right upper quadrant of the abdomen may at first suggest some acute intra abdominal pathology The avenues for the radiation of the chest pain are exactly those which are commonly seen in coronary thrombosis

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The time from the onset of the chest pain until the individual seeks medical advice is interestingly enough often 1 week and sometimes 3. This is explained by the extreme variability in the intensity of the chest pain. Some patients relate that they have only slight precordial pain; others are quite restless and anxious because of its severity.

It is my experience that in the majority of cases there is some augmentation of the chest pain with movements of the thorax and that bending forward at the waist often elicits an increase in the distress and a description of it as pulsatile. Respiratory movements also may aggravate the chest pain.

It can be appreciated that although chest pain is the most common symptom, nevertheless the variance in its description often makes it difficult to arrive at a diagnosis of pericarditis.[3,4]

There is no correlation between the duration of the chest pain and the presence of a friction rub as indicated by the number of patients in whom a friction rub is first heard after the chest pain has subsided, as well as by those patients in whom the friction rub outlasts the precordial distress by as much as 18 days. In about 50 per cent of the patients the pericardial friction rub is heard for at least several days beyond the time when the patient no longer has chest pain. The total duration of chest pain averages 10 days, with the extremes at 1 day and 6 weeks.

General symptoms of feverishness, chills, and mild sweats exist as part of the initial syndrome in two thirds of the individuals. Cough is characterized as dry and nonproductive and usually induces a marked increase in the severity of the chest pain. Cough is present in 75 per cent of the patients with perimyocarditis. Malaise is an almost universal complaint. Gastrointestinal symptoms in the form of anorexia and nausea are absent in the majority and certainly of minor importance when they do occur. Diarrhea is rare.

Antecedent respiratory infections are affirmed by approximately 50 per cent of patients, and the period prior to the onset of the presenting distress is usually 7 to 10 days. The evidence for this varies from an ill-described history of "head cold" to a more specific history of sore throat, rhinorrhea, and tender swollen cervical glands and slight cough.[5] In the remainder an initiating illness is unknown or forgotten.

A pericardial friction rub is most helpful to a proper diagnosis. This is present in 100 per cent of the cases.[6] It is to and fro in character, of moderately high frequency, and usually best heard in the left fourth and fifth intercostal spaces parasternally; the intensity increases with expiration and forward bending. However, the friction rub is quite easily heard even in the supine position with the breath held. The effect of respiration on the intensity of a pericardial friction rub has been a subject of controversy.[1,7,8] The lack of agreement among some observers may be accounted for by the failure to state the position of the patient at the time the murmur was heard. The increase in the intensity of many rubs with forward bending at expiration is probably related to the proximity of the heart to the anterior chest wall in such a position, as well as to the relative elevation of the diaphragm with slight compression of the pericardium from below.

Cardiac rate and rhythm present some interesting and in some cases alarming findings. A sinus tachycardia is noted in all patients sometime during the course of the disease and is usually present at the initial examination. Cardiac rate is not always proportional to the temperature, for in some patients it remains normal in spite of temperatures of 101°F or more. In others, rapid heart rates are found consequent to pain and too early ambulation.

Of more importance than cardiac rate are the arrhythmias which develop in about one third of the patients. It is quite reasonable to propose that the inflammation which must involve the atrial as well as the ventricular walls does cause single and multiple points of premature depolarization of the muscle. Thus atrial and ventricular premature beats and atrial fibrillation are seen. Of these irregularities, atrial fibrillation with its consequent diminished cardiac output and rapid ventricular rate calls for prompt therapy to control the ventricular response and especially so in those with known coronary artery disease.

or in the rare patient with extensive myocarditis

Other auscultatory findings correlate fairly well with the radiologic findings Daily examinations by the same observer will usually disclose some diminution in the heart tones This is explained in part by the x ray demonstration of cardiac enlargement presumably pericardial effusion In other words the physician should be able to suspect the development of a pericardial effusion However the same cannot be said concerning the subsidence of pericardial effusion The friction rub usually disappears after the effusion develops but since this interval may be as long as 8 days this relationship is probably no more than circumstantial Moreover the pericardial friction rub may still be heard in spite of a considerable accumulation of pericardial fluid confirmed by pericardiocentesis to be at least 750 c c in some instances Therefore it is concluded that although the diminution in heart tones and subsidence of a friction rub should make one suspect the development of a pericardial effusion the cognizance of such a possibility should not depend solely on these findings As pointed out by Harvey [7] the paradoxical sign of diminished heart sounds in the knee chest position as compared with the supine position may be of particular value in detecting moderate amounts of pericardial effusion However even in large effusions there may be no alteration in the intensity of the heart sounds

Fever with oral temperatures of over 100°F is present in most patients at the time of their initial examination and during their hospitalization daily rises to 104 F are not unusual Although 100 F to 102°F is the usual range no pattern is discernible A very few patients remain afebrile during the period of observation and give no history of an elevation of temperature prior to their hospitalization

Laboratory findings

By far the most important laboratory observations are the electrocardiogram and the chest x ray film However several other tests will be noted

Leukocytosis with absolute neutrophilia is present in 50 to 60 per cent of the patients on admission to the hospital [10] the remainder about half exhibit a neutrophilia in the absence of a total increase in leukocytes Counts as high as 17 000 cells per cubic millimeter are recorded but the usual is 10 000 to 12 000 cells per cubic millimeter

Anemia is not a feature of acute benign pericarditis and its presence suggests a more systemic disease

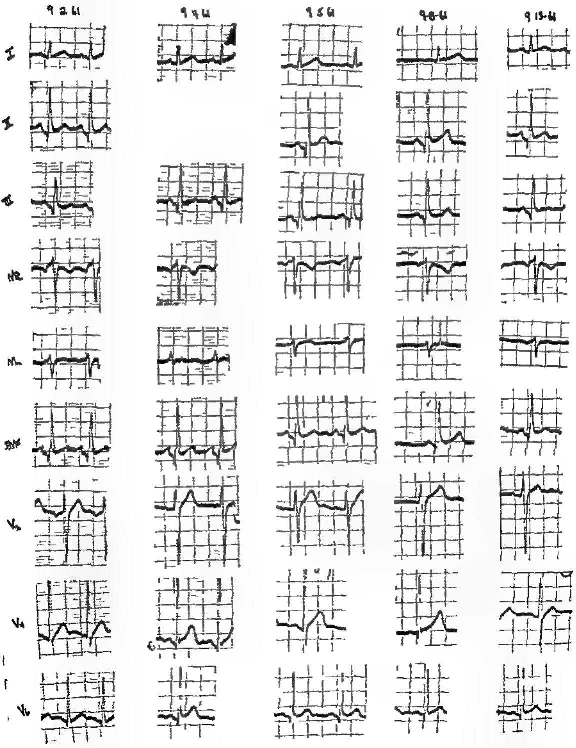
Erythrocyte sedimentation rate is nonspecific and is elevated during the acute phase of the pericarditis A return to a normal sedimentation rate is not to be used as an indication for ambulation of the patient This is especially true if steroids are being given

Serum enzymes are sometimes of diagnostic usefulness in the patient who presents with chest pain Serum oxaloacetic transaminase (SGOT) is normal in the uncomplicated cases of perimyocarditis and the value of such a test is quite apparent when one considers the confusion that sometimes arises in differentiating pericarditis from myocardial infarction [11] Serum lactic acid dehydrogenase has been slightly elevated in a few patients with perimyocarditis

Electrocardiographic means of substantiating a diagnosis of pericarditis is frequently unrewarding and the patterns obtained can vary from a normal tracing to those which give a suspicion of acute or chronic coronary artery disease The areas of the electrocardiogram which most often show alteration in pericarditis are the J point the S T segment and the T wave itself and these changes are not ascribed to the pericardial inflammation but rather to the underlying myocarditis which accounts for the current of ischemia and delay in subepicardial repolarization [13] The RST junction and S T segment displacement is seen only in the active state of the superficial myocarditis and therefore represents a greater degree of myocardial response than the T wave changes which can be seen even in the inactive state or the recovered stage and which by the way may persist for years and even for the remainder of the patient s life

The junctional point and the S T segment displacement is generally agreed to be the first change in the active state acute perimyocarditis [11] This may be f

in all the standard leads or just one or two leads depending on the electrical position of the heart. Standard Lead III and aVF reflect the S-T segment change in the vertically positioned heart with the vector more parallel to the respective lead. Precordial leads V_{2-4} overlying the cardiac muscle most directly show elevation of the S-T segment in the majority of cases. Lead V_1 as a rule has no elevation of the



S T se,ment The elevation mas extend to the more laterally placed precordial leads S T di placement over 3 mm and recipro cal changes suggesting infarction are ex ceptional

In the very early graphs in the individual ca e the T waves maintain their normal form although the elevation of the S T segment may lead one to misjudge this From this point on the electrocardiogram

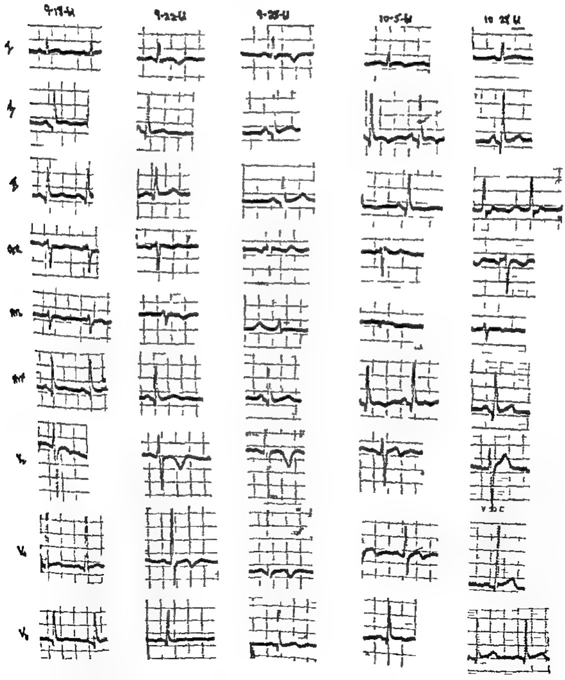


Fig 1 Serial electrocardiograms of a 26-year-old man are presented as showing typical changes during an acut pericardit s. The S-T segment elevation-wh ht but is followed in time by T wave changes and thi seen in the Lea I I and II and the p

Fig 2A Initial chest x ray films of a 26 year-old man It is to be noted that although the cardiac silhouette is enlarged the lung fields are relatively clear The lateral film shows the anterior and inferior accumulation of fluid

varies in both pattern and duration of accepted abnormality The S T segment may return to the isoelectric line bringing with it the still normally formed T wave In other instances the S T segment will return to its normal position and the repolarization of the myocardium may then show derangement in that the T waves will be progressively inverted with terminal inversion giving way to full reversal As implied the T wave abnormalities are generally seen in the same leads as the S T segment alteration The serial electrocardiographic changes that are proposed as typical are demonstrated in Fig 1 Only about 25 per cent of the cases show serial electrocardiographic changes that are typical Most individuals present themselves relatively late in the course of the illness and then only abnormalities in the T wave amplitude or direction are seen

Even though the electrocardiographic changes in acute perimyocarditis described above are typical a single electrocardiogram is not a firm basis for diagnosing this condition As mentioned the reciprocal S-T pattern of elevation in Standard Lead I and depression in Lead III might exceptionally be seen in perimyocarditis Furthermore T wave inversion in the precordial leads may be the only abnormality when the electrocardiogram is obtained late in the course of the pericarditis Is this T wave pattern in a single electrocardiogram one of impending infarction or is it truly the result of pericarditis? We can see that the diagnosis pericarditis may sometimes be one of exclusion There are however certain guides to the interpretation of the single electrocardiogram which favor ischemia rather than pericarditis As enumerated by Schwab and Herrmann[13] these are (1) S T displacement more than 4 mm (2) deep T wave inversion (3) monophasic wave formed by ST T wave fusion (4) pardee T wave (5) reciprocal S T segment displacement in standard leads Hull[14] states that there may be exceptions to (1) and (2) but that (3) (4) and (5) are very rarely misinforming

There is no evident correlation between the duration of the electrocardiographic changes and the duration of symptoms or clinical signs of the illness Most patients have a clinical course of 2 or 3 weeks and yet most electrocardiograms are still abnormal at the end of that period Furthermore there is no way of predicting from the electrocardiogram those patients who will have a more stormy course Electrocardiography therefore is used diagnostically and not as a prognostic tool

Chest x ray examination demonstrates signs consistent with pericardial effusion in most subjects with acute perimyocarditis My experience is one of a 73 per cent

incidence but others report only a 30 to 40 per cent occurrence[5,10]

How does one make a presumptive diagnosis from the chest x-ray film? It is obvious that the area of least resistance to expansion of the pericardial sac is located anteriorly and inferiorly Therefore the early accumulation of pericardial fluid will be most evident in the lateral chest film It should also be realized that the pericardial sac contains approximately 25 c c of fluid normally and that probably more than 250 c c of fluid must be present in the pericardial sac in the adult before the heart appears to be enlarged radiologically[1,16] Pericardial effusion with the patient in the erect position first causes the longitudinal axis to be enlarged and then with further effusion there is extension laterally and finally even posteriorly into the pericardial pouches What appears to be a collection behind the heart is actually the pericardial recesses extending laterally and posteriorly Pericardial fluid never accumulates behind the heart Figs 2 and 3 demonstrate varying degrees of pericardial effusion

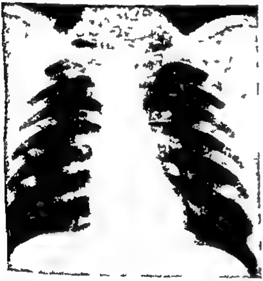


Fig 2B The same patient as in Fig 2A approximately 2 weeks later No pericardiocentesis has been performed

The rapidity of the enlargement of the cardiac silhouette in the absence of congestive changes in the lungs is of assistance in differentiating pericardial effusion from an extensive myocarditis which may give the same heart contour[illegible]

Enlargement of the cardiac silhouette is most frequently evident toward the end of the first week of the illness and usually shows signs of regression during the third week The size of the effusions is usually moderate but taps which yielded well over a liter of amber colored serofibrinous fluid have been reported[17]

The generalization can be made that those patients without demonstrable pericardial effusion have a much more benign course[6]

Fluoroscopy for the demonstration of diminished cardiac pulsations and changes in the cardiac configuration with the patient in the Trendelenburg position is unreliable The failure of the cardiac silhouette to change appreciably during the Valsalva or Muller maneuvers may be of some aid in distinguishing pericardial effusion from an enlarged and dilated heart

Venous angiography is rarely necessary In the case of doubtful effusion and when an aspiration of the pericardial sac is being considered such a procedure for the measurement of the right cardiac border may be done simply and be very reassuring

Approximately 65 per cent of the patients with pericardial effusions secondary to perimyocarditis have also x-ray evidence of pleural effusions the latter occur with equal frequency on the left and right sides These are usually small and ...

Fig 34 The initial chest x ray films of a 34 year old woman The lateral film demonstrates the commonly misinterpreted accumulation of fluid behind the heart There is also a pleural effusion at the base of the right lung

Viral studies consist mainly of the demonstration of neutralizing antibodies complement fixation and the isolation of the virus from blood stool and pericardial fluid There are prerequisites for assigning a viral etiology to acute perimyocarditis and by far the most important of these is the isolation of the virus[19] Isolation of the virus from the pericardial fluid is the surest means of diagnosis However this must be obtained early in the illness Undoubtedly time is one of the reasons for so many failures to isolate a virus from this source Serum obtained within the first week after the onset of chest pain affords the best opportunity for demonstrating a rising titer in neutralizing antibodies with subsequent specimens and therefore consistency with current infection A stable but elevated titer or a declining one is consistent with a recent infection with the particular virus or virus group A falling titer can be used in specifying the etiology[20]

Since most cases occur during an epidemic of a particular virus it should be evident that a significant percentage of the population will have positive stool cultures and elevated antibody titers in the absence of overt infection Notwithstanding numerous reports of tissue cultures *complement fixation titers stool isolation* and the like[1] assigning a virus as the cause and pericarditis as the effect in the individual case is presumptive Nevertheless the seasonal occurrence clinical picture and laboratory evidence of viral exposure all lend themselves to further definition of the entity known as *acute benign pericarditis*

Differential diagnosis

The discussion of a differential diagnosis of acute benign pericarditis is naturally based on an etiological classification of pericarditis

(I) *Infectious*—(A) bacterial (B) viral (C) spirochettal (D) fungal (E) parasitic

(II) *Noninfectious*—(A) Traumatic (1) direct (2) indirect (B) Nontraumatic (1) collagenous or hypersensitivity (2) metabolic (3) contiguous (4) neoplastic (5) others

Bacterial pericarditis sometimes presents a difficult differential problem However with the pyogenic variety the clinical course is usually one of extreme toxicity and there is historical or physical evidence of an antecedent infection such as pneumonia chest wound or abscess elsewhere with septicemia Cultures of the blood and purulent pericarditis will disclose the specific etiology

Tuberculous pericarditis is seldom recognized in the acute phase The paucity of symptoms and the presence of a peri

cardial effusion demand consideration of this diagnosis. Tuberculin skin test, sanguinous pericardial aspirate, thickened and irregular pericardium (demonstrated by injection of gas into the pericardial sac), positive cultures of the pericardial fluid and guinea pig innoculation are a few of the aids in this diagnosis.

Spirochetal pericarditis is secondary to the tertiary manifestations in contiguous

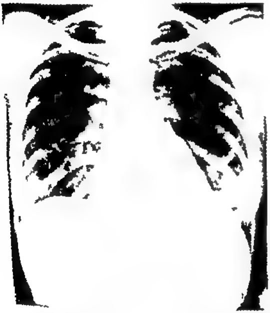


Fig. 3B. The same patient as in Fig. 3B 4 weeks later. A pericardiocentesis has been performed and 1,750 c.c. of fluid removed.

structures and can be dismissed since it is very rarely, if ever, an acute problem.

Fungal pericarditis usually occurs in endemic areas, and the occurrence of an acute pericarditis is rare. A more fulminant clinical course than that seen in viral pericarditis, skin tests, lymph node and other tissue specimens provide a means of diagnosis.

Parasitic pericarditis is accompanied by other signs of infestation such as amebic hepatic abscess and echinococcal cysts.

Viral pericarditis has already been included in the general discussion.

Traumatic pericarditis can be dismissed by the absence of recent surgery, history of recent instrumentation or injury to the thorax.

Collagenous or hypersensitivity syndromes form a relatively large group and require a greater search for distinguishing aids. Some of the more common types in this group are those of rheumatic fever, systemic lupus erythematosus, and that which occurs with serum sickness and allergic states.

The acute pericarditis of rheumatic fever is distinguished on the basis of other features of rheumatic involvement, such as lesions of the joints and skin, the presence of a prolonged P-R interval in the electrocardiogram, elevated C-reactive protein and antistreptolysin titer.

Systemic lupus erythematosus is of special note, and it is probable that, even in the absence of other manifestations of L.E., the female patient who presents with acute pericarditis, regardless of laboratory findings presumptive for a viral etiology, should be periodically examined for lupus erythematosus cells.

Serum sickness and allergic states are usually suggested by the associated symptoms and signs, history of exposure to an agent capable of inducing such a reaction, and the finding of eosinophilia.

Polyarteritis nodosa, scleroderma, and rheumatoid state are known to have been accompanied by pericarditis, but the systemic involvement is usually severe in such cases.

Metabolic pericarditis is most often seen in uremia. The presence of renal failure is not difficult to discover. The presence of pericarditis is merely an observation

course of the known renal failure and is not a problem in differentiating acute benign pericarditis

Contiguous disease may cause pericarditis Myocardial infarction with physical signs of pericarditis may be confusing in the early days of illness The differentiation from acute benign pericarditis is imperative if anticoagulation is to be used The fleeting nature of the pericardial friction rub with infarction and the serial electrocardiograms with reciprocal S T segment changes and the development of pathologic Q waves are helpful An elevation in SGOT practically excludes acute benign pericarditis

Neoplastic involvement of the pericardium may occur in the patient with malignancy When it occurs as the first sign of illness it may be perplexing because of its similarity to the sporadic case of acute benign pericarditis The rapidity with which effusion develops frequently requiring repeated pericardiocentesis and the finding of serosanguinous fluid demands cytological examination of the sediment Diagnosis is then provided

Other conditions of uncertain etiology are sometimes associated with pericarditis Some of these would be the postcommissurotomy postcardiotomy and postmyocardial infarction syndromes These are differentiated on the basis of the past history laboratory findings — electrocardiogram consistent with recent myocardial infarction for example—and the recurrent nature of the syndrome in the majority of patients

Patients with infectious mononucleosis may have an acute pericarditis but the enlarged lymph nodes abnormal lymphocytes on blood smear and the finding of an elevated heterophile antibody titer serve to distinguish this cause of pericarditis

The foregoing section on differential diagnosis serves to enumerate the more common forms of acute pericarditis It is not complete The classification is flexible The groups are not mutually exclusive

Complications

Complications of acute perimyocarditis are few in number and low in incidence

Tamponade from the massive accumulation of fluid should be suspected in any patient who demonstrates venous distention during the course of acute pericarditis One should not rely on the diminution of heart sounds or the decrease in apical impulse or even the pulsus paradoxus An enlarging cardiac silhouette during pericarditis and signs of venous congestion are indications for pericardiocentesis

Hemopericardium also as a cause of tamponade occurs spontaneously but must be emphasized as being much more common with the use of anticoagulants Suffice it to say that these drugs are contraindicated in the presence of an acute pericarditis

Congestive failure may result when acute pericarditis is superimposed on an already damaged myocardium and decompensation can complicate the usual benignity of this disease

Arrhythmias have already been discussed

Treatment

Complete bed rest is the best form of therapy for acute perimyocarditis In most patients with this condition the early institution of bed rest alone results in the prompt subsidence of symptoms Usually a total period of 2 or 3 weeks is sufficient However bed rest should be continued for a time beyond the disappearance of the friction rub Gradual ambulation is advised but if the patient has any recurrence of chest distress or elevation of temperature or cardiac irregularity it is wise to reinstitute the bed rest

Analgesics are seldom necessary beyond the first few days of hospitalization and morphine and the like are reserved for those patients whose chest pain is severe Sedation and reassurance are often ample substitutes

Antibiotics serve no role in the specific treatment of this form of pericarditis and should be used only for the concurrent and complicating bacterial infections

Cardiac glycosides and *quinidine* are used in the appropriate arrhythmias and details of their usage will not be attempted here Increased caution should be exercised if extensive myocarditis or tamponade is suspected

Steroids are by far the most dramatic form of therapy Their use may be warranted if the patient s general condition and temperature fail to respond to the customary measures Obviously all bacterial causes for such failure must be excluded

before the corticoids can safely be used. Prednisone in a dose of 10 mg every 6 hours is usually followed within 24 hours of its initiation by a marked general improvement: subsidence of temperature and a disappearance of the chest pain. The duration of this form of therapy must be individualized. Clinical observations have shown that the withdrawal of such medication must be in small decrements. The sudden cessation of steroid therapy in a patient with subsiding pericarditis is very likely to result in a "rebound" of chest pain and fever. The disappearance of the friction rub or pericardial effusion seems to bear no definite relationship to steroid therapy. Since most patients are managed quite satisfactorily simply with bed rest and sedation, and since there are always the possible complications of steroid therapy, such medication is not recommended for routine use.

Prognosis

With regard to prognosis, several questions might be asked. Does so-called acute benign pericarditis ever result in constrictive pericarditis? In Wood's experience[3] and Carmichael's series of 50 cases,[24] this did not occur. Does perimyocarditis result in significant myocardial fibrosis? What role, if any, does this natural irritant play in promoting an increase in coronary vascularity? These questions are unanswerable at the present time. It must be concluded that the immediate prognosis is very good, but that the ever present threat of severe arrhythmias and cardiac tamponade demands careful observation and prompt treatment. Recurrences within a period of 2 to 3 months are not uncommon but are usually milder than the initial episode.[24]

Summary

A resumé of the condition known as *acute benign pericarditis* has been presented. Seasonal incidence, sporadic cases with histories of acute respiratory infections prior to the onset of chest pain, and the increasing number of reports of positive viral studies suggest a virus to be the cause in the greater percentage of cases. Stress phenomena and autoimmune reactions are also recognized as etiological possibilities.

The importance of the early diagnosis of acute pericarditis lies partly in its confusion with myocardial infarction and the dangers of anticoagulant therapy. The complications of cardiac tamponade and cardiac arrhythmias demonstrate that in some instances acute benign pericarditis is far from benign.

Therapy for the uncomplicated case is discussed. Corticoids, although dramatic, must be used cautiously.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Hydralazine in hypertension

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The drug 1 hydrazinophthalazine or hydralazine was introduced as a specific treatment for hypertension in 1950 when its hypotensive effect was discovered to be associated with renal vasodilatation Despite some favorable reports hydralazine has not been generally accepted because of acute side effects such as headache nausea vomiting flushing tachycardia increased angina and chronic toxicity manifested by a syndrome which is indistinguishable from disseminated lupus erythematosus Moreover it is not effective in all patients with tolerance occurring in some of those initially benefited English authorities list the drug among those now little used Recent evidence however indicates that hydralazine is a relatively safe and useful antihypertensive agent if administered under appropriate conditions

In a recent long term large clinical trial hydralazine chlorothiazide and reserpine administered alone or together in various combinations were compared with placebos in a double blind evaluation The effects of these agents on basal blood pressure during long term treatment clearly demonstrated that hydralazine in conjunction with chlorothiazide or reserpine or both exerted a significant antihypertensive effect The combination of all three agents was superior to any two producing an average reduction of 30 mm Hg in the basal diastolic pressure of patients with moderately severe hypertension as compared with a slight rise in blood pressure in the placebo treated control subjects

When hydralazine was used in combination with reserpine and chlorothiazide the subjective side effects such as headache and palpitation which are commonly associated with it when it is used alone were not prominent No instance of chronic toxicity characterized by the rheumatoid lupus syndrome occurred in approximately 250 patients who received hydralazine in a daily dose of 200 mg continuously for periods of 6 months or longer These results are to be compared with an incidence of 7 to 12 per cent of the lupus syndrome in patients receiving large doses of 500 mg per day or higher as reported in the past by other investigators

Hydralazine by a peripheral mechanism not yet understood produces a vasodilatation which is limited to the arterial side of the circulation Venous dilatation and the resulting orthostatic hypotension do not occur The antihypertensive effect of the marked arterial vasodilatation is partially counteracted by the cardiac actions of hydralazine which include an increase in heart rate and output These opposing cardiotonic effects tend to be neutralized however by reserpine which reduces cardiac rate and by the saluretic agents which lower cardiac output The subjective side effects of palpitation and ta hy

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cardia which result from the cardiac action of hydralazine also are reduced by the addition of these other agents Such pharmacologic considerations provide a rational basis for the use of combinations of antihypertensive drugs

The risk of serious toxicity from hydralazine is minimal if the daily intake does not exceed 200 mg In the author's experience doses as small as 25 mg twice daily are effective in some of the milder cases of hypertension when the drug is added to saluretic agents and reserpine although in general somewhat higher doses are required

Present evidence indicates that hydralazine should not be given alone but should be added to other medication for patients who do not respond to saluretic agents or reserpine or both The initial doses of hydralazine should be small in order to avoid acute side effects Ten or 12 5 mg twice daily increased gradually over a period of several weeks to 25 mg twice or three times daily and then if necessary and if well tolerated to 50 mg will minimize the occurrence of subjective side effects In the few patients who show no response r 150 mg or at most 200 mg per day more potent agent such as guanethidine should be substituted A generally satisfactory regimen used by me has been 100 mg of chlorthalidone plus a maintenance dose of 0 25 mg of reserpine taken together once daily to which hydralazine may be added if an additional antihypertensive agent is required Many patients including some with severe hypertension can be controlled quite adequately by this method without orthostatic hypotension and without the necessity for blocking agents which usually require meticulous dosage adjustments

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Annotations

The cervical venous hum

The cervical venous hum is an innocent continuous murmur which can be found in the majority of healthy children and adolescents.[1] It was probably described by Laennec[2] and its clinical significance was indicated by Palmer and White.[3] Its importance is derived from two considerations: first, that it is so common; second, that it may be confused with such pathologic causes of continuous murmurs as arteriovenous fistula and patent ductus arteriosus. Despite its frequent occurrence, many courses in physical diagnosis do not describe this murmur and many recent medical graduates are ignorant of its existence. In the following paragraphs we shall discuss cervical venous hum from these aspects: (1) location and quality, (2) incidence, (3) confusion with other varieties of continuous murmurs, and (4) relation to thyrotoxicosis.

The cervical venous hum is a continuous murmur with diastolic accentuation. Unlike the murmur of patent ductus arteriosus, there is usually no silent interval between the end of the murmur and the first heart sound. The murmur is usually loudest beneath the sternal attachment of the sternocleidomastoid muscle just superior to the medial end of the clavicles. It may be bilateral or unilateral. When unilateral, it is more common on the right side. In most instances it is audible when the patient sits or stands and disappears or becomes very faint when he lies down. The murmur can be accentuated or brought out by turning the head away from the side being examined or by elevating the chin. The murmur can almost always be eliminated by moderate pressure over the internal jugular vein a few centimeters above the clavicle. This amount of pressure does not interfere with carotid arterial pulsations. Very light pressure may increase the intensity of the murmur. The Valsalva procedure causes the murmur to disappear.

A few years ago we made a study of the prevalence of the cervical venous hum in subjects of all ages. The murmur was found to be especially common in children between the ages of 5 and 15 years. In this group it was detected in 95 per cent of those who were examined in the sitting posture. When these children lay down, the murmur was audible in only 3 to 5 per cent. In children under 5 years of age and in young adults the murmur was present or could be produced in 75 per cent of those examined. In the older age groups the murmur was less common but could be elicited by proper positioning of the head in 50 per cent of the subjects in our study. A similar frequency of venous hums in children was found by Landis and Kaufman.[4] Jones[5] found a cervical venous hum in 27 per cent of healthy older subjects between the ages of 14 and 76 years.

Especially in children, the cervical venous hum murmur may be audible over the upper anterior thorax as well as in the neck. In our series the murmur was heard in either the first, second, or third anterior intercostal space in 10 to 19 per cent of the subjects who were in the age range between infancy and 49 years. The murmur was not found inferior to the third intercostal space. In many instances hasty or inexpert examination has caused confusion of this murmur with that of a pathologic disorder. Frequently when the murmur is well heard in the first and second left intercostal spaces an erroneous diagnosis of patent ductus arteriosus is made.[7] When the venous hum is loud in the second right intercostal space, a diagnosis of aortic insufficiency may be proposed.[8] Cary[9] has reported the case of a 37 year old woman wh

the internal jugular vein Thus one is led to question the existence of a separate *continuous* murmur arising in the thyroid gland although an arterial *systolic* murmur may be found

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A computer program for automatic analysis of electrocardiograms

For the past several years there has been increasing interest in automatic analysis of medical data by digital computer To develop such procedures computer programs are required which state in mathematical language the methods and criteria to be applied to given problems Development of efficient programs is a major task comparable with the design of new recording equipment Usually complex filtering procedures are necessary for the separation of signals and noise Furthermore criteria for the detection and elimination of artifacts and transformation of the signals to an intelligible and meaningful readout are necessary Input and output format memory space available in the computer and computation time need to be considered in such developments

Fortunately once a program is written and properly checked it can be used on any other computer of the same type Usually only minor modifications of the program are necessary for application *to other* types of machines with comparable or higher capacity *This leads to a standardization of* analytical procedures which is as desirable as standardization of recording equipment

In the field of automatic data processing computer *analysis of electrocardiograms* has received particular attention There is certainly a need for such procedures which is illustrated by the following typical application

1 Large epidemiological studies include frequently electrocardiograms Very seldom is a sufficient number of trained cardiologists available for interpretation of thousands of records Distribution of the tracings to a number of interpreters leads almost always to subjective differences and bias in *the evaluation of the record* Computer programs however lead to a high degree of consistency because the same principles of analysis are applied throughout application

2 The same degree of consistency is achieved in mass screening programs of large population groups Follow up studies over long periods of time become feasible and open new ways for research in the early diagnosis of heart disease

3 Many ECG measurements such as time integrals eigenvectors curves of spatial magnitude orientation and velocity are too tedious and time consuming to obtain by hand They can be easily obtained by a properly programmed digital computer This leads to an evaluation of advantages and disadvantages of various procedures in a search for optimal parameters for ECG analysis

4 *Eventually the new method may lead to* computer analysis of electrocardiograms on a routine basis Such a practice would relieve the physician of a large amount of tedious and time consuming work *Before this can be done however the physician needs to learn how to evaluate correctly* computer outputs A neat and decisive output obscures too easily the fact that the result of any analysis cannot be better than the information which is supplied It will always remain the physician s task to integrate ECG information with other sources of clinical information whether analyzed by hand or computer

The computer program described here is intended for use with any corrected orthogonal lead system It can also be applied to any other lead system if three not too closely related leads are recorded simultaneously *Results however have to be in*

terpreted differently. The leads are recorded in analog form on magnetic tape. Subsequently they are digitized by means of a special purpose analog-to-digital converter. The sampling rate used in the program is 250 per second. Such a sampling rate is sufficient for all measurements except for high frequency components. Higher sampling rates can be easily obtained if sufficient memory space is available in the computer. A slower sampling rate can be handled also if desired. Rates as low as 150 per second can be considered to be sufficient for not too exacting application.

The program was written originally for digital records which contained only one cardiac cycle starting and ending in the T-P interval. These cycles had been selected visually during the analog to digital conversion. This program has been modified later to handle records of arbitrary length as far as memory space is available. Thus, selection of the best cycle of a long record for further processing has become possible. Furthermore, each cycle can be processed and compared with the others for analysis of arrhythmias.

The program package consists of a main routine and a set of subroutines. The main routine selects analytic procedures to be performed and controls the sequence of operations. Subroutines are used for computational and bookkeeping procedures. Three types of subroutines are used:

1. Input routines. These select records from a given sample, read the records in from a tape of raw data or data which underwent preliminary processing.

2. Output routines. These set up proper output format for printout or transfer of results to output tapes or cards. Further processing such as statistical analysis can be accomplished with the data in this format.

3. Analytical routines. As preliminary step, each lead is first multiplied with a scale factor in order to obtain magnitude values expressed in millivolt (calibration). Subsequently, a filtering procedure eliminates high frequency noise. The beginning and end of P, QRS, and T complexes can be determined by means of a timing program after the filtering procedure. Once the ECG waves and intervals between them are properly identified, a wide variety of measurements can be performed. The determination of time integrals, polar vectors, eigenvectors, instantaneous vectors at given time interval, and scalar amplitudes and durations of P, Q, R, S, T waves have been described in more detail previously.[1] Scalar components can also be transformed into spatial parameters plotted as curves of spatial magnitude, orientation, and velocity.

The described programs have been made available on request. They are coded for the IBM 7090 digital computer. For the most part, they are written in Fortran II language which can be adapted without too many changes to most large and medium sized computers. Memory requirements depend upon the length of the ECG record to be processed and the number of analytical subroutines used for complete analysis. A memory of 8,000 computer words will be satisfactory for most cases. As mentioned above, three simultaneously recorded ECG leads are required as input. These leads need to be available in digital form, i.e., analog-to-digital conversion equipment is needed for obtaining such a digital format.

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An implantable cardiac pacemaker allowing rate control

This annotation concerns 3 cases and details the authors' experience in the development of an implantable pacemaker which could be imbedded at one operation but which possesses the optional extra of external control of the discharge rate of the generator unit.

The first case reported is that of an 81-year-old man who was treated in January, 1961. He had a history of Stokes-Adams attacks which became more frequent just prior to hospitalization; these were associated with long periods of unconsciousness and failed to respond to conventional medical therapy. The heart, which was irregular, had a rate of 20 per minute on admission, and the blood pressure was 160/125 mm. Hg. There were no signs of congestive cardiac failure or of recent myocardial infarction. An electrocardiogram recorded during an attack indicated complete ventricular standstill.

Bipolar stainless-steel wire electrodes, which protruded 5 mm. from a casing of silicone rubber 2 cm. by 1 cm. by 1 cm., were inserted into the anterior aspect of the ventricular myocardium overlying the septum near the base of the heart. The insulated leads from the electrodes were taken into the anterior abdominal wall through the sternal attachment of the diaphragm and were attached to an external pacemaker ...

liminal voltage such as has been found with unipolar electrode systems The pulse rate before operation had varied from 25 to 44 per minute between attacks Attempts to increase the rate above 50 per minute were poorly tolerated as judged by the decline in the systolic blood pressure

After operation there were no more period of cardiac stand till and a current of between 3 and 5 Ma at between 1 0 and 1 5 volts produced complete pacing of the ventricle Toward the end of the first postoperative week foul purulent putum appeared and the patient s general condition rapidly deteriorated He died 8 days after operation Necropsy revealed bilateral staphylococcal absces es in the basal lobes of the lungs There was chronic pyelonephritis with left ventricular hypertrophy The coronary arteries were mildly atheromatou with much narrowing of the circumflex branch of the left coronary artery 2 cm from its origin

Dr R B Goudie of the University Department of Pathology We tern Infirmary Gla gow showed by serial ection that there was fibrosis of the atrioventricular node which in his opinion was enough to account for the conduction defect So far as the electrode sy tem and the site of implantation into the heart were concerned all appeared to be sati factory

During this period we had elaborated a prototype of our implantable pacemaker which was inserted into a 50 year-old man who re ponded in a sati factory fashion to thi model Our next ca e presented before further model were ready so that ...tment was by implantation of an Elema type rate generator

... second patient a 61 year old woman with ... pressure of 210/115 mm Hg was ho pital... with attacks of loss of consciousnes which were at fir t confu ed with epilepsy Later the correct diagnosis was made intermittent complete heart block during which her heart rate fell to 22 beats per minute although her pulse between attacks was normally maintained on sinu rhythm at 70 to 80 beats per minute Despite an adequate trial of medical therapy her attacks continued and resulted in her becoming bed bound An Elema type of generator was successfully implanted in June 1962 and she has been free of attacks since although a premature battery failure associated with a substantial increase in pacemaker rate nece itated replacement of the generator in October 1962 Since then he has had no further trouble

Shortly after thi ca e another patient (Ca e 3) became available This third pati nt a 54 year-old man had an anteroseptal myocardial infarction in 1953 with re idual right bundle branch block He made a good recovery and had not been troubled with angina or dyspnea of effort His only complaint was occa ional precordial discomfort accompanied by a sensation which he described as low churning feeling in his chest associated with con iderable lightheadedness and faintness

In 1958 he lost consciou ness completely during one such attack, and thi recurred 6 weeks and again 10 days before hi admi ion to the hospital when on risin to urinate during the night he became aware of an irregular slow heart action and fainted His doctor found that his pulse rate was between 35 and 40 per minute The patient again felt the churning sensation in his chest during these attacks He was admitted to the Southern General Hospital on Oct 15 1962 with no evidence of congestive cardiac failure but his heart rate was slow—25 per minute His blood pressure was 120/60 mm Hg There was no cardiac enlargement but he had the clinical and auscultatory signs of complete heart block An electrocardiogram showed complete A V block (atria 85 per minute ventricles 33 per minute) and evidence of an old anteroseptal infarction The ventricular pacemaker eemed to be situated somewhere in the upper left ventricle

Treatment consisted of ephedrine 30 mg every 8 hours for 5 days and then isoprenaline 20 mg every 6 hours which was increased after several days of recurrent Stokes-Adams attacks to 20 mg every 4 hours He was put on steroid therapy 4 days after admission but after a week on betamethasone he had not significantly improved On one day he had seven moderately severe Stokes Adams seizures By this time he was also showing evidence of mild congestive failure and treatment with diuretics and digoxin wa cautiously started

At this point the decision was made to review the situation The patient was only 54 year old Drugs were not influencing his attacks and much in his past history suggested instability of hi conducting system There was no evidence of a recent infarction to account for the present attacks

We decided therefore to implant a cardiac pacemaker Thus on November 1 after a preparatory period during which steroid were stopped and congestive failure corrected a Pye pacemaker was implanted in the subcutaneous tissues of the left hypochondrium with electrodes placed 2 cm apart on the upper anterior aspect of the left ventricle well clear of the main coronary arterie There was no untoward reaction during the operation and the patient made a good recovery

By means of an external control unit the ventricular rate was maintained at 30 to 40 beats per minute for 4 to 5 days and allowed to come up to the inherent pacemaker rate of 60 per minute after a week The maintenance of peripheral blood pressure was used as one of the indications that the increase in rate was not excessive The patient was discharged from the hospital after 6 weeks without evidence of cardiac failure and having had no further Stokes Adams attacks His pulse rate was 60 per minute and regular except for a very occasional extrasystole He remain well and has now returned to work

Since this article was written a fourth patient a 68 year-old woman with intermittent complete heart block has been treated successfully by implantation of the Pye type of generator

The authors have discu sed[1] the types of pacemaker available and come to the conclusion that an acceptable machine should be implanted at one operation Its discharge rate should preferably be at 60 to 70 beats per minute In elderly patients in particular it is important that there should be no external impedimenta which may affect pacemaker discharge by movement From Case 1 the authors concluded that a person with block and persistent bradycardia should not be switched suddenly into

a fast speed on a fixed rate generator and therefore justify the value of their design of control unit in slowing the rate of discharge particularly in the first postoperative week

The main problems to be solved in designing the implantable pacemaker were (1) long term electrical reliability (2) the best packaging for the least weight and volume (3) a reliable plug and socket between the leads (4) a mechanically and electrically reliable lead and (5) temporary external control of pulse rate

Electrical reliability is a function of the number of components The Pye pacemaker contains a complementary transistor astable multivibrator circuit containing two transistors four resistors three condensers and five batteries The external control is accomplished through a tuned circuit and crystal rectifier producing an auxiliary bias voltage for the multivibrator circuit By suitable packaging of the components a weight of 3 5 ounces has been placed in a volume of 2 8 cubic inches The pacemaker will deliver a 5 volt pulse across 1 000 ohms at a rate of 60 per minute for about 3 years Pulse width is 2 msec

The connection between the leads and pacemaker which must be proof against body fluids is a large area low-contact pressure screw joint The body fluids are excluded by coating the lead end with a thin film of silicone grease and also by the pressure of the silicone rubber case on the end of the lead (this is a precaution against the possibility of faulty administration of the silicone grease)

The lead and electrode is a major problem in pacemaker reliability and a multi helix stainless steel polyethylene insulated lead with a flat slightly convex platinum disc electrode (for good tissue-electrode contact pressure) was chosen The electrode is 0 375 inches in diameter and 0 125 inches thick The multi helix design was attractive because a number of conductors in parallel give an added safety factor

By means of a control unit and an externally applied coil mounted in a silicone rubber pad the pulse rate may be reduced to about 40 pulses per minute without the need of taking out leads through the skin and thereby incurring the risk of infection

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Cardiovascular diseases
New etiological considerations

It has recently been proposed [illegible] despite certain apparent contraindications [illegible] that various cardiovascular disease might be fundamentally autoimmune in character The suggestion is based upon a consideration of age and sex specific mortality rates as a function of age

Mortality statistics have attracted much attention in theoretical studies of human carcinogenesis (see Reference 4) but they have been almost totally neglected in discussions of the etiology of non neoplastic diseases Cancer mortality [illegible] in general steeply age dependent indeed age specific mortality rates from all cancers combined are approximately proportional to the sixth power of age over much of adult life All the hypotheses that have been advanced to account for this striking relationship have two features in common (1) carcinogenesis [illegible] a multistage process and (2) each stage is initiated by the occurrence of a random event No alternative to the multistage stochastic interpretation has been offered The idea that neoplastic initiation depends upon a small number (≥ 2 and generally ≤ 7) of random primary events is easy to accept because it is known that a single transplanted cell c[illegible] propagate a tumor in an immunologically receptive host animal A few somatic mutations and/or infective agents concentrated in a single cell might well promote a neoplastic transformation Neither [illegible] it difficult on this view to account for multicentric tumors [illegible]

Unfortunately—or so it at first appears—a [illegible] similar type of dependence of mortality on [illegible] found when we examine statistics for cardio[illegible] diseases In several categories (International Abridged List 1955 [illegible] B2[illegible] B25 B[illegible] B28 and B29) age-and-sex specific mo[illegible] are accurately proportional to a const[illegible] age over an appreciable part of the [illegible] relationships suggest [illegible] these diseases [illegible] be the consequence of accumul[illegible] random events The validity [illegible] each pathogenic [illegible] might to [illegible] respect to age [illegible] total [illegible] erally be les[illegible] tion seems [illegible] Superf[illegible] of cells a[illegible] because [illegible] body as [illegible] apone[illegible] to ch[illegible] all [illegible] example

obvious how statistics and mathematics can be reconciled with pathology

Burnet's forbidden clone type of hypothesis[6,7] provides an elegant escape from this dilemma. If one or a few random changes in a stem cell can generate a clone containing a very large number of cells then in principle we have a mechanism which can *amplify* a small number of events into a widespread *systemic disease*. We have to imagine that cells in the forbidden clone(s) synthesize pathogenic agents—for example enzyme hormones viruses or antibodies—that are capable of entering the blood stream and attacking target tissues. Is there any reason for suspecting that the actual pathogens could be autoantibodies?

Observational experimental and theoretical deductions[2,4,10] indicate that in some human autoimmune diseases at least the *primary* pathogenic agents are cell bound autoantibodies carried by small lymphocytes. If Burwell's hypothesis[1] of the role of lymphoid tissue in morphostasis is valid it is to be expected that any tissue that is in any way *subject to mitotic control by lymphocytes* might under appropriate conditions be subject to autoimmune attack. The number of diseases known or suspected to be autoimmune has increased rapidly in recent years and it will be surprising if this process of discovery is already exhausted. In particular there would seem to be no good *a priori reason for excluding cardiovascular tissues from* such consideration.

Of special significance to the present discussion is the conclusion[2,9,3] that in normal people—but in agammaglobulinemic ones—an endogenous defense mechanism against forbidden clones of lymphocytes exists and that this is mediated through humoral antibody. In other words cell bound autoantibodies are themselves autoantigenic.[12] The clinical severity of a morbid autoimmune disease depends upon stress factors—including infection—and it is inferred that these modify the efficiency of the defense system. We should expect *that certain dietary factors and for example the concentration of calcium ions in plasma* might influence both the primary autoimmune attack and also—and especially—the effectiveness of the immune defense against forbidden clones. Further more this defense process appears to be more efficient in women than in men[10] and it manifests itself in two ways.

Firstly when the events of an autoimmune disease is related to the number of genetically identical forbidden clones (as in rheumatoid arthritis) more such clones are required on the average to elicit a given clinical grade of the disease in women than in men.[11] Secondly the average interval or latent period between the completion of the last somatic mutation and the clinical onset of a morbid disease is longer in women than in men.[2]

In both cases these sex-differences are associated with a steeper age-dependence of the disease in women than in men. *With the exception of chronic* rheumatic heart disease this characteristic is revealed in the mortality statistics for cardiovascular diseases listed above.[4] The absolute mortality rates are however lower in women. Again chronic rheumatic heart disease is the exception[4] and it resembles *recognized autoimmune* disease in showing generally a preponderance in women. It has been suggested that this sex difference could be indicative of either (a) the inheritance of a dominant predisposing allele on the X chromosome or less probably (b) a single somatic mutation affecting a gene on the X chromosome. (The X chromosome *appears to play an important role in autoimmunity and in immunology generally*.[1,2,13])

Hence age and sex specific mortality statistics for various cardiovascular diseases reveal characteristics that are compatible with an autoimmune etiology. It still does not follow that these diseases are autoimmune—some other system may well possess properties similar to those of the immune system. However the first requirement of a working hypothesis is that it should be able to account for the known facts; another requirement is that it should suggest further critical observations and experiments.

On the present view we would predict that in *homologous organ transplantation*—where incompatibilities between graft and host are common—there should be frequent evidence of immunologically induced changes in the vessels of the transplanted organ. It is noteworthy therefore that a common cause of failure of kidney transplantation in man is an obliterative vascular change which has *been attributed to an immune attack*.[15] The hypothesis that cell bound autoantibodies are the primary pathogens in certain cardiovascular diseases should of course be tested in organ culture experiments.

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Book reviews

AN ATLAS OF CONGENITAL HEART DISEASE. By Frank F. Sherman, M.D., Associate Professor of Pathology, University of Pittsburgh School of Medicine and Associate Pathologist, Children's Hospital, Pittsburgh, Pa. Philadelphia, 1963, Lea & Febiger. 263 figures, 303 pages. Price $15.

This atlas was compiled from the Museum of Congenital Heart Disease at the Children's Hospital of Pittsburgh. As such, the flora of congenital heart disease of the entire area of Western Pennsylvania can be studied in the 503 specimens reviewed.

The manner of presentation is anatomic with a stress on individual lesions. An introductory chapter deals with a statistical evaluation of the cases presented and a method of dissection. The author then deals with anomalies of (1) venous return, (2) coronary arteries, aorta, ductus arteriosus and pulmonary arteries, (3) the atrial septum, (4) the ventricular septum, (5) transposition of the great vessels, (6) malformations of valve, and (7) endocardial fibroelastosis and the heart in congenitally disturbed metabolic states. The descriptions are very succinct and the illustrations are good, being views of actual specimens, diagrams and drawings. The references are of recent authors.

This is a very useful book for those who are interested in anatomy or for those who wish to acquire a sound basis in anatomy for clinical work.

DAS HERZ DES MENSCHEN. Band I and II. By Prof. Dr. W. Bargmann, Direktor des Anatomischen Institutes der Universitat Kiel, and Prof. Dr. W. Doerr, Direktor des Pathologischen Institutes der Universitat Heidelberg. Stuttgart, 1963, Georg Thieme. 299 illustrations. 1,155 pages.

The book, subdivided into two volumes, consists of 17 chapters by 19 German authors. According to Bargmann and Doerr's foreword, there was no German book available which gave the theoretical basis of the whole field of cardiology for clinical therapeutic application. Diagnosis and therapy are not included in the work, which is limited intentionally to a presentation of the organic characteristics of the heart (*Organcharakter des Herzens*) in normal and pathologic conditions. Although diagnosis as such is not included, many parts of the book have rather immediate diagnostic application. According to the intention of the author, the book is more than a textbook and less than a handbook. This means that the content of several chapters has been presented in greater detail in recent reviews and articles, but it is undoubtedly a great advantage to give a cross section of the basic information of the various fields of cardiology together in one or, as a matter of fact, two volumes.

As is often the case in a cooperative effort, not all fields are presented in the same detail. The book leans toward the anatomic-morphologic-histologic (including electronic microscopy) aspects. Of particular value for the heart surgeon is the chapter on topography of the heart (K. H. Knese). The chapter on cardiac ontogenesis gives the basis for the extensive discussion of cardiac malformations and congenital heart disease (K. L. Goerttler). In this respect the book approaches a handbook. Goerttler published in 1958 (Georg Thieme Verlag, Stuttgart) a monograph on the normal and pathologic development of the human heart from which a part of the illustrations was reproduced.

Normal (E. Bauereisen) and clinical physiology of the heart are competently represented, but several gaps are noticeable. The paucity of electrocardiographic illustrations (and comment) contrasts with the abundance of morphologic illustration. Although electrocardiography could not (and need not) be presented in any great detail in view of the availability of numerous good textbooks, it is clinically a standard method, and the absence of electrocardiographic illustrations of myocardial infarct, bundle branch block (except schematic diagrams), several basic types of arrhythmias, A-V block, WPW, etc., appears to be a defect. These conditions are discussed in the text. The presence of most types of arrhythmias and conduction disturbance cannot be demonstrated and their mechanism explored without the electrocardiogram. Burger and Lohmann discuss the age changes up to 90 years with emphasis on the biochemistry, but this short chapter of 8 pages (with only 28 references) hardly does this important aspect justice.

However, this should not detract from the great merit of this volume. It is an extremely valuable reference work for the shelf of any cardiologist. The reproduction of the numerous illustrations (in part colored) is excellent. The volume is introduced with a fascinating chapter of 20 pages on "Historical Highlights in the Exploration of Heart and Circulation" (K. Rothschuh). On the title page is a reproduction entitled "Sudden Death" from the tomb of Seti (Egypt) 3000 B.C. Illustrations from the original publications of Leonardo da Vinci, Harvey, Bertholini, Weber, Waller and others are reproduced.

KORRELATIONEN ZWISCHEN HAMODYNAMIK UND HERZSCHALL. By Hans Helmut Wolter. Basel, 1963, S. Karger. 73 illustrations. 156 pages. American distributor: Albert J. Phiebig, P. O. Box 352, White Plains, N. Y. Price $10.50.

A small part of the mechanical energy of cardiac contraction is converted into sound. This book is a thorough analysis of the hemodynamic causes for this transformation of energy. Thus heart sounds and murmurs are analyzed in respect to the various phases of the cardiac cycle in simul-

taneous record of pressure in the atria, ventricles, pulmonary artery, and aorta. Heart sounds occur at *the abrupt ending of kinetic* phases by the valves and walls, whereas in the initial phases (i.e. beginning of ejection and beginning of diastolic filling) the energy is used up for the acceleration of the blood volume, so that no condition for the generation of heart sound normally exists. On this basis the change in heart sounds is analyzed and correlated with the changes in hemodynamics in valvular disease and arrhythmias. Although the energy for heart sound is derived from the contractile energy of the myocardium, the energy for heart murmur is derived from the flow velocity.

The source of energy for the systolic murmurs is of course the contractile tension, whereas for diastolic murmurs the source of energy is the stored elastic tension in arteries and veins (Windkessel). The author differentiates for the systolic murmur between *Druckaustreibungsgeräusche* (primarily due to changes in pressure) and *Volumenaustreibungsgeräusche* (primarily due to changes in volume). The term *Druckaustreibungsgeräusche* is not quite correct even for the German language, since *Druck* (pressure) is not *ausgetrieben* (ejected). Nevertheless, such differentiation as to underlying causes is valuable. The pressure sounds parallel the changes in pressure, reaching their peak in the middle or end of systole, whereas volume sounds (associated with large stroke volume) have their peak in the initial part of systole. Extracardiac vascular murmurs are analyzed in respect to hemodynamic factors, elastic properties, and peripheral resistance. This short outline may suffice to give an idea of the character and purpose of the book. It is divided logically into two main sections: heart sounds (pages 18 to 85) and heart murmurs (pages 86 to 141).

The author concludes that the numerous variations in heart sounds and murmurs are diagnostically useful reflections of the underlying hemodynamic changes, so that it is often possible to predict intracardiac and intravascular changes in pressure from the phonocardiogram. It should be mentioned that the correlations are observations on simultaneous pressure and sound records in individual patients and not a statistical analysis of correlation (except Figure 35 for the interval between second heart sounds and mitral opening snap and mean pulmonary capillary pressure). The illustrations are excellent and the book is a valuable addition to the phonocardiographic literature.

Studies on the Electrocardiogram of the Race Horse. By J. D. Steel, B.V.Sc., Senior Lecturer in Veterinary Medicine, Faculty of Veterinary Science, University of Sydney, N.S.W., Australia. Sydney, 1963. Australasian Medical Publishing Company Ltd. 48 pages. Price £A2 2 0.

The study reported in this short monograph was undertaken with the intention of aiding the identification and study of d[illegible] f the heart which occur in race horses. Serial electrocardiographic recordings obtained in 306 race horses were reviewed and analyzed statistically, although fulfillment of the aims of the work was impeded by a necessary paucity of necropsy material. Criteria of normality were proposed and the findings were also related to racing performance—a positive correlation between length of QRS interval, heart weight, and ability to win races was noteworthy.

The nature of a possible infective origin of the interstitial myocarditis which occurs in horses was discussed. Such horses had shown a fall-off in performance with electrocardiographic changes and the etiology was debated in the light of a detailed histologic study of 16 such cases.

Those readers who are fascinated but frustrated by the human cardiomyopathies will be interested to read about myocarditis in the race horse.

Arterial Hypertension and Ischaemic Heart Disease: Comparisons in Epidemiological Studies. By Alex M. Burgess, Jr., M.D., Consultant, Cardiovascular Diseases, WHO; Zdenek Fejfar, M.D., D.Sc., Chief, Cardiovascular Diseases, WHO; and Aubrey Kagan, M.B., M.R.C.P., D.P.H., Medical Officer, Cardiovascular Diseases, WHO. Geneva, 1963. The World Health Organization. 36 pages. Price 30 cents.

This pamphlet was prepared as a report of the Cardiovascular Section of the World Health Organization. It emphasizes the magnitude of ischemic heart disease and arterial hypertension as a cause of death and the need for well organized studies designed to elucidate the etiology by large scale population studies. Problems in handling such studies are discussed and recommendations for future studies are made.

Initial Heparin Therapy as a Supplement to Peroral Anticoagulants in Acute Myocardial Infarction (Norwegian Monographs on Medical Science). By Erik Enger, Alf Chr. Julsrud, and Knut Kirkeby. Philadelphia, 1963. F. A. Davis Company. 49 pages. Price $3.95.

This paperback pamphlet, previously published as a Supplementum to *Acta Medica Scandinavica*, presents findings which refute the value of initial heparin therapy as a supplement to peroral anticoagulants in acute myocardial infarction. Although they began with a basic group of 306 patients, through various criteria for exclusion the authors finally worked with 219, of whom 102 received heparin and 117 did not. Heparin was administered in equally spaced (in time) injections 4 times daily for the first 3 days of admission. Hypocoagulability of the blood during this period was not tested. With this regimen the results suggested that heparin increased the risk of bleeding, may have alleviated the chest pain, but was ineffective in preventing thromboembolism or death.

The authors indicate their opinion th

ideal study on the value of anticoagulant therapy in myocardial infarction has not yet appeared a thought which few unbiased students of the problem would dispute Perhaps the very nature of the special problems involved in obtaining controls for such a study will continue to preclude its definitive performance in human beings It is unfortunate that their publication which purports to include a survey of the literature lists only 37 references for a field which by now has many times that number Readers interested in compiling an exhaustive file of references on the subject of anticoagulants should include this work

MEDICAL ELECTRONICS IN CARDIOVASCULAR DISEASE (A special three part symposium reprinted from *Progress in Cardiovascular Diseases*) Edited by Charles K Friedberg M D and Ephraim Donoso M D New York 1963 Grune & Stratton Inc 274 pages Price $10

This volume is a collection of 16 papers by 32 authors presented in a three part symposium Six papers on the application of analog and digital computers indicate the interest in these new electronic tools but probably overemphasize their immediate importance in cardiovascular research

The first paper Introduction to Medical Electronics emphasizes that medical electronics involves not only instrumentation but also electromagnetic field theory electrical circuit theory sonics electronic components electronic computers control systems information theory communications system and recording and reproducing The importance of the inverse situation the application of biology to engineering is mentioned

The papers on computers range from a review of the field to specific applications of the analog computer in a circulation model and of the digital computer in cardiovascular epidemiology in the diagnosis of congenital heart disease and in the analysis of the electrocardiogram and the phonocardiogram

Cinefluorographic equipment applications of ultrasound electrocardiographic instrumentation vectorcardiographic equipment the measurement of instantaneous blood flow densitometers pressure transducers and telemetry are the subjects of the other papers

As is to be expected in such a volume the depth and breadth of coverage of the various areas varies among the papers and certain areas receive little or no mention However necessary details can generally be found in the numerous references listed in each paper

This book can be recommended for a quick look at many of the applications of electronics in cardiovascular studies

Announcements

A postgraduate course on CARDIOVASCULAR DRUG THERAPY sponsored by the Department of Medicine Hahnemann Medical College and Hospital will be given January 20 23 1964 at the Marriott Motor Hotel Philadelphia Pa

The purpose of this symposium is to evaluate the current cardiovascular armamentarium The rationale and drug spectrum of antihypertensive drugs antianginal compounds diuretic agents vasopressor anticoagulant and antiarrhythmic drugs and cardiotonic compound will be explored in relation to their clinical pharmacologic application

Address inquiries to Miss Sage Rosen Executive Secretary Postgraduate Education Hahnemann Medical College and Hospital 230 North Broad St Philadelphia 2 Pa

THE IVTH EUROPEAN CONGRESS OF CARDIOLOGY will be held in Prague Czechoslovakia on August 17 to 22 1964

To submit abstracts or for any information concerning the Congress please write to Hanus Kafka M D General Secretary IVth European Congress of Cardiology Karlova Namesti 32 Prague 2 Czechoslovakia

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Editorial

On teaching pharmacology and therapeutics in our medical schools

Deliberation upon and a rephrasing of an article by John J. Abel

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John Locke wrote, "You cannot imagine how far a little observation carefully made by a man not tied up to the four humours, sal, sulphur and mercury, or to acid and alkali which has of late prevailed will carry a man in the curing of diseases thought very stubborn and dangerous and that with very little and common things and almost no medicine at all." Reflecting upon this statement John Abel wrote in 1900, "In an age in which pathology and diagnosis are so far advanced and in which more genuine help is derived from the rational use of drugs than ever before in the history of medicine, haphazard drugging is unpardonable, but still more to be condemned is a fanatical and conceited adherence to dogmas based on a superficial understanding of complex physiological principles."[1]

How far have we advanced in our clinical therapeutic practices since the remarks of Abel? Certainly today diagnosis and pathology show the effects of an immense number of advances since the time of Abel's statement. One has only to attend the CPC (Clinical Pathological Conference) to see the astute senior medical student arrive at a diagnosis that the pathologist will confirm from anatomical examination at autopsy. However, quite different from the 1900 period, today the patient is likely to have had several concomitant anatomical pathological finds that are diagnostic of the existence of more than one disease process. There are likely to be symptoms that are physiological and biochemical that cannot be confirmed by anatomical examination. This change in the CPC has been largely brought about by advances in our knowledge of the basic medical sciences and by the use of improved therapeutic procedures that produce relief from classic disease symptoms and prolong life.

This increase in the use of therapeutic regimens has not been without problems. A recent review refers to a large number of diseases which would not have occurred if sound therapeutic procedure had not been employed.[2] The emergence of a second disease due to sound therapeutic procedures is a *nemesis* to the physician. A *dilemma* that the physician may face with the use of drugs is a condition in which the therapeutically effective dose and the toxic dose for a drug overlap. One is impressed with the possibility that a superficial under

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Received for publication [illegible]

standing of complex physiological principles seems to exist in many cases in which the physician is faced by a *nemesis* or a *dilemma* In the last 20 years our understanding of the complex physiological and biochemical principles of drug therapy has approached the immense advances in diagnosis and pathology yet the teaching of these principles has not made the same strides It appears that this superficial understanding of complex physiological principles in some instances may be the result of a separation of the basic medical sciences and clinical medicine Much like parallel lines these two disciplines pursue their courses and seldom cross

What is the purpose of the basic medical science course in pharmacology?

According to Abel an astute clinician a hundred years ago 1865 justified his studies of the effects of drugs and morbific agents on the surviving umbilical artery by the following words Moreover it is not to mere clinical experience that we must look for a revelation of the laws of disease The laws of chemistry were not discovered blazing fire or crumbling rocks the laws of hydrostatics and hydraulics were not revealed in torrents tides or ocean currents nor those of pneumatics and electricity in winds whirlwinds and thunderstorms much less could it be rationally expected that the laws of pathology should be discovered amid the much greater complexity and more multitudinous conflicts of elements presented to the physician at the bedside of a diseased or dying patient It is the laboratory and by artificially contrived experiments that the clue has ever been spun the torch lighted to guide through the labyrinths which hide the arcana of nature

The major purpose of the basic course in pharmacology is to demonstrate in detail by artificially contrived experiments how drugs act on the various organs of the body what their *specific therapeutic effects* are, and what their general effects are on the compound mechanism man Thus we attempt to teach the beginning student in medicine conceptions resolved into their elements The student learns a logical thought process to be used in dealing with drugs

These concepts are thought to be familiar to the experienced therapeutician However due to the lack of adequate contact the teacher of pharmacology is likely to be unaware of important areas that could be useful to the student furthermore a careful study of empirical therapeutic advances might also contribute to the fundamental knowledge of drug action On the other hand the empiricist may argue that the clinical fact is sufficient and that a demonstration of the mechanism of the drug action is unnecessary A practical minded physician can safely use drugs However sooner or later he will find himself faced with a problem directly concerned with the welfare of his patient that can only be answered by a fundamental understanding of the mechanism of action of the drug and the underlying physiological and biochemical changes that occur with the disease and the therapy of the disease No branch of practical medicine can afford to neglect the study of the principles and methods of the other whether this be clinical medicine or basic medical science

The teachings of pharmacology are not always immediately convertible to useful information for the physician at the patient s bedside An objective of pharmacology is the teaching of conservatism by pointing out how vastly complex are the phenomena of the action of drugs and by showing how little is clearly understood aside from the grosser and visible changes occurring in disease and following the administration of drugs Therefore the dogmatic use of cardiac stimulants depressants antipyretics and other remedies in the symptomatic treatment acclaimed in commercial circulars finds no justification in the teachings of pharmacology however neither pharmacology nor the other basic medical sciences should give support to the unthinking worship of canonical authority Concepts which have proved to be useful in diagnosis and therapy of disease without supporting basic scientific evidence should be carefully investigated at the basic science level since the success of the agent may point to an important advance in our fundamental understanding

How do we achieve the purposes of the teaching of pharmacology?

The modern medical center should be primarily concerned with public health in a comprehensive significance. In the triangle composed of care of the patient, teaching and research, research and teaching should form the base for excellence in the care of the patient. In medical school teaching, the basic medical scientist who is a worker in the laboratory, who follows attentively the researches of his contemporaries and who observes good care of the patient will be able to clear up doubtful points in the textbook, anticipate future advances in special areas, and is likely to have the advantage over the author of the textbook in certain areas, for no man is able to cover the whole ground with equal authority. The basic medical scientist should attempt to contribute as well as observe in the clinical area. This contribution should be restricted to the information gained from the artificially contrived experiments which might be useful to the physician. This collective search for wisdom between the basic medical scientist and the applied scientist should greatly reduce the empirical use of concepts in dealing with the individual patient. The concept usually deals with a disease or is applied to a grouping of patients; however, each patient is an individual problem. Basic science teaching should extend not only into the last two years of medical school but into the internship and residency as well, since this is the last opportunity for formal contact of the practicing physician with the fundamental sciences.

What are our objectives in training pharmacologists?

While the teaching of a medical student should ever have the goal of excellence in care of the patient as its ultimate aim, the teaching of a graduate student in the basic medical sciences should be primarily concerned with the fundamental precepts of his area. It is necessary that the individual keep his identity as a clinician, biochemist, physiologist or pharmacologist. The major portion of the student's and the teacher's time should be given to acquiring and dispensing knowledge in his special area in accordance with the fundamental precepts of his area. As John Abel has said of the pharmacologist, "as elsewhere, judgement and special knowledge are required, and the day has long passed when he who knows the drugs of the pharmacopeia and their clinical uses and who is able only to set up a kymograph and attach a few registering instruments can claim to be a pharmacologist. Such a one will not travel far beyond the region of mere routine, a region chiefly of pedagogical interest." If we do not maintain our separate precepts, our separate thought processes and our separate underlying motivations, the advances in our fundamental understanding will likely suffer. It is only a man of unusual powers and exceptional training in science who can successfully combine practice with the demands made on the fundamental investigator in the basic medical sciences as an investigator and teacher.

What should the motivation of the faculty be to accomplish these objectives?

It is not believed necessary that the basic medical scientist be engaged in medical practice, nor is it thought that all of the members of the basic medical science departments take part in the clinical teaching. Most of the members should devote their time to advancing fundamental knowledge in their chosen fields without regard to application. By the same logic it is not necessary that the clinician become involved in fundamental research. Clinical research and care of the patient more readily prepare him for his medical teaching duties. A few teachers holding joint appointments in clinical and basic science departments could act as "moderators" between their specialties and the other disciplines. When this individual is a basic medical scientist, he should work closely with the clinical research program, make ward rounds, attend conferences and contribute fundamental knowledge. Interested clinical faculty members should be encouraged to have joint appointments in the basic medical science departments to contribute clinical information to the medical school courses in these areas, to assist the basic investigator in the application of his data to clinical problems, and to provide graduate students in the basic sciences with fundamental points of clinical medicine which will aid the student in his career development as a medical teacher.

For many years the medical tea

the basic sciences and the clinical areas were teachers first and researchers second Their research was aimed at providing information of a nature directly concerned with their problems as medical teachers Today most of the instructional staff are medical scientists engaged in research greatly removed from their teaching areas Teaching becomes a side line It is not thought that this arrangement is necessarily bad However it should be pointed out that there is an obvious greater separation between acquired knowledge and application The advances in knowledge are not being incorporated into practice as rapidly Therapeutics is the prime example of this deficiency A thorough knowledge of scientific therapeutics based upon pharmacological principles and an understanding of materia medica is rare today Although considerable time is given to pathological diagnosis based upon history symptomatology and laboratory findings little attention is given to therapy beyond the use of a trade name preparation This preparation is usually a mixture of compounds In many cases the physician is not sure of the drugs in the mixture or the dosage More and more emphasis is being placed upon knowledge gained from circulars distributed by drug manufacturers and advertisers and contacts with salesmen and less and less upon contact with pharmacologists experienced medical school therapeuticians and scientific journals The student s contact with pharmacology is usually limited to one semester Many schools do not have therapy as a course in the third or fourth year The teaching of therapeutics is limited to a direction to use this or that drug with no indication as to the difference in the compounds or to their actions Dr George Burch has recently re-emphasized the importance of the choice of drugs the selection of dosage the timing of administration and withdrawal the determination of the route of administration knowledge of the therapeutic pharmacological effect knowledge of side effects toxicity and route of elimination In modern therapy these parameters must all be 'played and balanced with the same sensitivity precision and complex integration that the painter or conductor uses when he works with his materials This may well be the origin of the term *the art of medicine* but a more adequate description would be *the science of medicine* [4]

The motivation of the faculty engaged in the teaching of pharmacology and therapeutics must be aimed at correcting this tragic loss of good therapeutics - control to commercialism It can be said that the proper use of a drug requires complete diagnosis But it can also be said that once diagnosis is established the physician s responsibility is not ended Good therapy is essential since incorrect therapy only adds to the complications Just as those members of the faculty who are primarily concerned with pathology and diagnosis must spend their time teaching the student to reach the correct and complete diagnosis the pharmacologist and therapeutician must spend their time teaching the student the elements of correct and complete therapy

What can be accomplished by special lecture series and joint research efforts?

It has been pointed out that many more serious errors are committed by physicians and surgeons in the use of drugs than during surgical procedures [4] Errors in surgery are self revealing the offender is readily identified and the evidence direct Drug therapy is engaged in considerably more often than is surgical correction and in many cases greater judgment is necessary for the proper use of drugs Yet one finds that considerably more time is spent at conferences on matters which pertain to diagnostic signs the anatomical pathological findings the natural history of the disease the number of patients seen in a year with the disease and a host of other *ramifications in regard to the disease* and little time is given to matters pertaining to therapy As Dr Burch says good therapy cannot be learned from books conferences and seminars alone but requires the indulgence of the physician But he points out that these measures are indispensable *and that there is a need for* training in therapeutics given by those who know and practice good therapy [4]

In addition to a greater discussion of therapy at existing conferences a few didactic lectures should be given as the need arises and the interest is presented

in the clinical and basic science areas. These need not be regularly scheduled lectures but rather scheduled at a time when the interested students and faculty can attend. These lectures would review and supplement the material present in either the basic pharmacology course or in the clinical sections. This approach would not burden the individual who wants only a passing knowledge of a particular subject, but would give the student who elects to go deeply into the subject an equal opportunity to do so. In each case the discussions should be more thorough. They should contain, in addition to the generic and trade names of drugs used and their dosage, the pharmacology of the compound. This would include route of administration, desired pharmacological effect, side effects, toxicity, duration of action, route of elimination, and special reference to any particular effect that would make the compound contraindicated. Synergistic or antagonistic actions when the compound is used with other agents should be pointed out.

Just as there is the year for pathology, we believe that pharmacology deserves additional time. Careful consideration should be given to the use of this time. Pharmacological principles as well as drug actions should be taught. The CPC serves a useful purpose for diagnosis. A clinical conference on therapy should serve a similar useful purpose in therapeutics. The history of medicine has dictated a greater emphasis on diagnosis based upon pathological anatomical findings. Today more emphasis is being placed on physiological findings. The biochemical tests are becoming increasingly useful. Pharmacology provides the information necessary for correction of these physiological and biochemical symptoms. Preventive pharmacology is an advancing field. Is it not time to teach therapeutic diagnosis? For surely today the patient who has not received good therapy *can* complain despite the fact the diagnosis agreed with the autopsy report.

Joint research projects will provide a common interest for the fundamental pharmacologist and the clinical investigator. The project will provide for a greater application of the knowledge gained from the research but more important it will bring together the parallel lines of basic science and clinical medicine. It will form the common ground that allows successful conferences, seminars and short courses. These individuals who will group together to work on research will find that they can group together and teach. Yet each will keep his separate identity as clinician or pharmacologist.

Summary

There is a need for scientific advancement in the care of the patient. The basic science elements of care of the patient are largely covered by inadequate courses in the first two years of medical school. This leads to empirical use of concepts and hampers the physician at the patient's bedside.

Needed improvement in medical school teaching can be met by joint appointments between the basic science and clinical departments. Basic science teaching by basic scientists at all levels should be limited to fundamental elements. The clinical faculty should mold these elements into concepts to be used in the care of the patient.

The clinical faculty should aid in the basic science departments in the direction of the medical student in his first two years. They should offer clinical instruction to the basic science student who plans to teach in the medical school.

Joint research projects will provide the greatest application of fundamental knowledge. The clinical problems can be resolved in artifically contrived experiments and the knowledge gained in the experiments can be evaluated in regard to clinical concepts.

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Unusual forms of second-degree atrioventricular block, including Mobitz Type-II block, associated with the Morgagni-Adams-Stokes syndrome

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The Morgagni-Adams-Stokes (M-A-S) syndrome occurs most frequently with complete heart block[1-4] and rarely with sinus bradycardia.[4-6] However, between attacks the electrocardiogram often displays varying degrees of second-degree heart block, especially 2:1 block, or only first-degree heart block with bundle branch block. In a review of 100 consecutive cases of M-A-S syndrome over a period of 15 years, from 1946 to 1961, at The Mount Sinai Hospital, New York, several forms of second-degree atrioventricular (A-V) block were noted which are generally regarded as being unusual.

There were 3 cases of Mobitz Type II block in our series and 7 additional cases were reviewed from the literature.[7-10] Two patients in our series demonstrated 2:1 A-V block with A-V interference associated with the M-A-S syndrome, and 8 patients had advanced or high degrees of A-V block. This report deals with the clinical and electrocardiographic manifestations and the prognostic significance of these uncommon forms of second-degree heart block.

Mobitz Type II block

There are two forms of Mobitz atrioventricular block. Mobitz Type I is commonly termed the Wenckebach phenomenon. Mobitz Type II has not been consistently defined since the original publications of Mobitz on this subject.[7,11] The classification into Types I and II actually corresponded to Wenckebach's division of second-degree block.[1] In Type I, according to Wenckebach's concept, dropped beats were presumed to be due to impaired atrioventricular conduction, as indicated by a prolonged P-R interval (actually a prolonged a-c interval in the jugular pulse). In Type II, dropped beats were presumed to be due to impairment of ventricular excitability, since the P-R interval was within normal limits. Subsequent evidence revealed that, despite the normal P-R interval, cases of Type II second-degree heart block were also associated with lesions in the bundle of His and presumably with impaired atrioventricular conduction. In the original reports of Mobitz,[11] Type II included second-degree block of varied severity, e.g., 2:1 and more advanced heart

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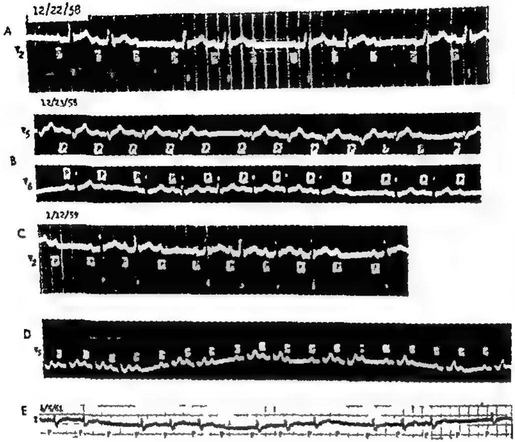

Fig 1 Mobitz Type II block A B C Patient No 1 J H (Table I) A demonstrates 3:2 Mobitz Type II block in which the P-P and P-R intervals are fixed. Following every third P wave the ventricular beat is dropped. B demonstrates a 6:5 Mobitz Type II block in Lead V5 and a 6 ventricular response in Lead V6. C was taken 20 days later and again shows 3:2 and 5:4 Mobitz Type II block. D Patient No 2 G K (Table I) Demonstrates regular sinus rhythm before development of 3:2 and a 2:1 Mobitz Type II block. E Patient No 3 S S (Table I) Shows a 4:3 Mobitz Type II block.

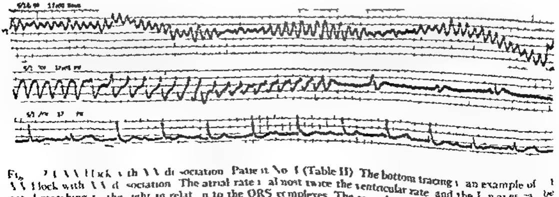

Fig 2 A V block with A V dissociation Patient No 1 (Table II) The bottom tracing is an example of A V block with A V dissociation The atrial rate is almost twice the ventricular rate and the P waves ... marching ... in relation to the QRS complexes The second and the last QRS complexes are examples of ventricular capture beats. The QRS complexes are supraventricular in form The tracing at the top shows ventricular fibrillation followed by ventricular tachycardia in the middle tracing The third complex from the end in the middle tracing is a ventricular escape beat and the last one is a ventricular capture

block provided that the P-R interval was normal. In recent times[8,10] and in this communication, Mobitz Type II block has been more strictly delimited to that form of second-degree A-V block in which the P-R and P-P intervals are fixed and a single ventricular beat is dropped at intervals without warning, resulting in a 3:2 or 4:3 or 6:5, etc., ventricular response.[7] This unusual form of atrioventricular block is of special interest because of the consistent occurrence of Adams-Stokes syndrome in patients with this type of conduction disturbance and because an ominous prognosis has been attributed to it.[8]

Data on the 3 patients in our series who manifested Mobitz Type II block transiently are presented in Table I. In only 1 patient (No. 1, J. H.) did the 3:2 block persist throughout the entire electrocardiogram. In subsequent records in this case there were 5:4, 6:5, and 7:6 ratios of Mobitz block (Fig. 1,A, B, C) before complete heart block developed. This patient had a severe form of the M-A-S syndrome with frequently changing degrees of heart block, and he remained in the hospital 6 months. He died suddenly 1 year later at home.

Patient No. 2 (G. K., Table I) had a transient 3:2 Mobitz Type II block (Fig. 1,D). Her electrocardiogram returned to regular sinus rhythm before complete heart block developed. She had frequent M-A-S attacks, but the electrocardiogram eventually returned to regular sinus rhythm after periods of incomplete and complete A-V block. Her disease became so severe that it was necessary to implant an internal cardiac pacemaker. She is still alive 2 years after the onset of the M-A-S syndrome and 7 months after the pacemaker was installed. Before the development of complete heart block, both Patients No. 1 and No. 2 had a right bundle branch block. With complete heart block, their electrocardiograms showed QRS patterns of both right and left bundle branch block. The characteristic similarity in these 2 cases was the frequently changing block (Table I).

In Patient No. 3 (S. S., Table I) there was a regular sinus rhythm with right

Table I. Mobitz Type II A-V block

Author	*Patient*	*Age Sex*	*ECG*	*Mobitz Type II block*	*Changed to*	*P-R (sec.)*
Mobitz[7]		55 M	3:2 A-V block to CHB	3:2, 4:3	NSR	
Spang[8]		45 M	2:1 and 3:2 A-V block	3:2	NSR	0.36
Kaufman et al.[9]	J. C. R.	41 M	CHB to 3:2 Mobitz with diaphragmatic myocardial infarction and RBBB	3:2	3:2 Mobitz persisted	0.16
	D. C.	67 M	NSR with tall R-V1 and wide QRS plus left axis deviation (on admission) to Mobitz Type II block	5:4, 4:3, 3:2	CHB	0.20
Katz[10]	(a)		Not demonstrated	3:2, 4:3		0.24
	(b)		Not demonstrated	6:5		0.26
	(c)		Not demonstrated	2:1, 3:2, 4:3		0.24
This series No. 1	J. H.	67 M	NSR with RBBB to Mobitz	3:2, 5:4, 6:5, 7:6	NSR to CHB with LBBB	0.20
No. 2	G. K.	67 F	NSR with RBBB to 3:2 Mobitz with RBBB	3:2	2:1 to NSR to CHB with RBBB and LBBB	0.20
No. 3	S. S.	68 M	NSR with RBBB to 2:1 with RBBB to Mobitz	4:3	NSR with RBBB	0.12

NSR, Normal sinus rhythm. CHB, Complete heart block. ASHD, Arteriosclerotic heart disease. RBBB, Right bundle branch block.

bundle branch block 2 1 A V block and 4 3 Mobitz Type II block on different occasions (Fig 1 E) Regular sinus rhythm reappeared and persisted This patient has had a milder course than did the other 2 patients and he is still alive 6 months after discharge from the hospital

All 3 patients with Mobitz Type II block demonstrated other forms of incomplete A V block and in no instance did the second degree A V block persist

The etiology in Patient No 1 was coronary heart disease The other 2 patients one aged 67 years and the other 68 had no evidence of angina pectoris myocardial infarction hypertension or valvular heart disease and therefore are classified as having heart block of unknown etiology

Seven cases of Mobitz Type II block have been recorded in the literature available to us [7-10] In addition Wenckebach published jugular and radiopulse tracings which indicate occasional dropped beats with a normal constant a c interval but no electrocardiograms and no clinical history are given [1] Three out of 100 patients in our series with M A S syndrome presented this form of block The A V ratios in these 3 cases were 3 2 4 3 5 4 6 5 and 7 6 None of the Mobitz Type II blocks observed by us or reported by others persisted except in the case of 3 2 block reported by Kaufman and associates [9] The M A S syndrome occurred in 7 of the 10 cases of Mobitz block In the other 3 cases or electrocardiograms depicted in the monograph on arrhythmias by Katz and Pick[10] there are no clinical data and we do not know whether the patients experienced M A S attacks Thus the M A S syndrome has occurred in all cases of Mobitz Type II in which the clinical history was reported and it would be of interest to observe whether this is an invariable association or whether Mobitz Type II block occurs independently in patients who never experience M A S attacks

No specific pattern for Mobitz Type II block exists since the ventricular beats drop out without warning Eight examples of 3 2 four of 4 3 two of 5 4 and of 6 5 and one each of 7 6 and 4 3 A V block occurred in the 10 patients The patients

P P (sec)	R R (sec)	QRS (sec)	M A S syndrome	Severity	Course	Etiology
0 48		Wide	Ye	No follow up	Survived	Not commented on
0 68 0 74	0 68 0 70	0 16	Yes	Not mentioned	Survived	ASHD
0 63	0 63	0 13	Yes	50 attacks in a few days	Survived remained asymptomatic with a 3 2 Mobitz block	ASHD with acute MI
0 64	0 64	0 16	Yes	Several severe attacks	Died	Cor pulmonale
		0 08			No clinical data	
		0 17			No clinical data	
		0 14			No clinical data	
0 68	0 68	0 14	Ye	Severe	Survived hospital Died 1 year later	Coronary heart disease
0 60	0 60	0 17	Yes	Severe	Survived but required internal pacemaker	Unknown
0 64	0 64	0 12	Yes	Mild	Survived	Unknown

LBBB Left bundle branch block

with 6 5 and 7 6 A V block are the first examples of these ratios to be reported In all but one case the QRS complex was widened The sudden dropping out of the QRS has been attributed to a prolongation of the absolute refractory period of the A V bundle the relative refractory period is unchanged [7,10]

The serious prognostic significance which has been attached to this type of A V conduction[7,9] is justified to the extent that it has been associated with the M A S syndrome However we cannot conclude that the outlook differs from that in other cases of A V block with M A S syndrome since all 3 patients with Mobitz Type II block survived the period of hospitalization Two of the 3 patients are still alive 6 and 30 months after the onset of their disease but 1 patient died within 12 months after the M A S syndrome developed An awareness of this condition plus more frequent and longer electrocardiographic tracings will probably disclose more examples of Mobitz Type II block and provide more definite information as to its clinical and prognostic significance

2 1 A V block with A V interference dissociation

In this arrhythmia the atria and ventricles respond to independent pacemakers (A V dissociation) not because of depressed A V conduction as in complete heart block but because the A V node or the ventricles are usually refractory when the sinus impulse arrives (interference) Occasionally the sinus impulse arrives at a nonrefractory period and elicits a ventricular response (capture beat) However in addition to such interference dissociation there is a concomitant depression of the atrioventricular bundle which would have resulted in 2 1 A V block if there were not a simultaneous interference with conduction due to the refractory period when the atrial impulse arrives

The criteria employed for the diagnosis of 2 1 A V block with A V interference dissociation[11] are (1) a ventricular rate greater than 30 per minute with a constant R R interval (2) an atrial rate which is a multiple of the ventricular rate and almost double its frequency (3) a "supraventricular" form of QRS of less than 0 10 second duration (4) the presence of ventricular capture beats (5) a minimum critical R P interval (absolute refractory period) which is constant and (6) no retrograde V A conduction The minimum critical R P interval is the minimum required time between a conducted sinus impulse and the immediately preceding automatic A V nodal beat Two patients out of 100 in our series fulfilled these criteria

Patient No 1 had a changing heart block with periods of 2 1 A V block complete heart block and regular sinus rhythm as well as 2 1 A V block with A V dissociation The atrial rate was 65 per minute and the ventricular rate was 33 with a minimal critical R P interval of 1 02 seconds and QRS duration of 0 10 second Her course was marked by recurrent M A S attacks due to ventricular tachycardia and fibrillation but her electrocardiogram continually reverted to regular sinus rhythm (Fig 2) Patient No 2 had a milder course The atrial and ventricular rates were 83 and 40 per minute respectively with an R P interval of 0 66 second and QRS of 0 10 second Both patients had ventricular capture beats but no retrograde conduction One patient had hypertensive and coronary heart disease whereas the etiology of the cardiac disease in the second patient was unknown One patient died 3 years after the onset of the M A S syndrome whereas the other patient is still alive at a 3 year follow up

Although there is some controversy as to the interpretation of such cases[14,15] we believe that 2 1 A V block with A V dissociation is a distinct entity and have 2 cases out of 100 in this series which fulfill the criteria They did not present a clinical picture which differed from that in other forms of heart block Although digitalis is reported to be a cause of 2 1 A V block with A V dissociation[11] neither of these patients had received digitalis

Advanced atrioventricular block

Advanced or high grade atrioventricular block is a form of second-degree heart block in which several successive atrial impulses are blocked resulting in an A V ratio of more than 2 1 usually 4 1 and 6 1 whereas the odd numbered forms 3 1 and 5 1 are generally regarded as being

rare Usually the ventricular rate is below 50 per minute [9,10] and there may be atrial flutter or tachycardia

Eight out of 100 patients demonstrated high degrees of A V block 3 1 A V block occurred in all 8 in 2 there was also 4 1 block and in 1 5 1 A V block (Table II)

These multiples of A V block were transient in every case and each patient demonstrated complete heart block during his course (Fig 3 A and B) Four patients (50 per cent) remained in complete heart block and the other 4 (50 per cent) resumed a normal sinus rhythm In all 8 cases the electrocardiogram showed a bundle branch block pattern in 3 there

Table II Ad anced A V block

Patient	*ECG*	*BBB*	*Form of advanced A V block*	*Etiology*	*Severity of M A S synd ome*	*Duration of M A S syndrome*	*Patient on digitalis*	*Course in hospital*
1 O P	2 1 3 1 A V block to CHB with LBBB	Ye	3 1	ASHD	Severe	2[1] yr	No	Survived
2 J H	NSR with RBBB 2 1 3 1 and Mobitz Type II to CHB to NSR with 1st-dgrree block	Yes	3 1	ASHD	Severe	6 mo	No	Survived
3 A P	NSR with LBBB to 2 1 3 1 4 1 5 1 to CHB to NSR	Yes	3 1 4 1 5 1	ASHD	Severe	4 yr	No	Survived
4 R R	NSR with LBBB to 3 1 4 1 to CHB	No	3 1 4 1	ASHD	Severe	4 wk	No	Died
5 D S	NSR with RBBB to 2 1 3 1 to CHB to NSR	No	3 1	H and ASHD	Moderate	1 yr	No	Survived
6 J K	CHB to 2 1 3 1 to NSR with RBBB	No	3 1	ASHD	Moderate	2 wk	No	Survived†
7 F O	2 1 3 1 with RBBB to CHB	No	3 1	Unknown	Severe	1 wk	Yes	Died
8 W L	2 1 3 1 with RBBB to CHB	No	3 1	H and ASHD	Moderate	3½ yr	No	Survived for 3 yr (follow up)

D ed 6 m ths l t r t h me
†D ed 12 m ths l t at h me
H Hypert n Oth r bb vi t a n T ble 1

Fig 3 Advanced A V block Patient No 3 A P (Table II) A demonstrates a 3 1 A V block which [sub]sequently developed into complete heart block B shows A V block starting at 5 1 decreasing to 4 1 and the 3 1 in the same lead

was left bundle branch block and in 5 right bundle branch block in association with the high grade A V block In 2 of the patients there was an incomplete A V block with right bundle branch block and later a left bundle branch block pattern of the QRS with complete heart block developed A third patient had left bundle branch block initially but this changed to a right bundle branch block pattern with complete heart block

Although all of these patients had moderate to severe M A S syndrome only 2 (25 per cent) of the 8 died in the hospital Three patients died within 1 year after discharge and the other 3 are still alive after 1 year 1 year and 3½ years respectively

With one exception they all had coronary heart disease and 2 patients were also hypertensive In only 1 did advanced A V block develop as a result of digitalis which is usually considered to be a common cause of this condition

Although the odd numbered forms of advanced A V block are considered to be rare [18] 8 patients in our series demonstrated a 3 1 A V block and 2 of them also had 4 1 block and 1 had 5 1 block No example of 6 1 A V block was noted Therefore in this series the odd numbered forms are more common than the even numbered types This may be coincidental but it is also possible that the odd numbered forms of advanced heart block are unstable relative to the even numbered forms and may be more likely to be complicated by pacemaker failure and M A S These advanced degrees of block were all transient and progressed to complete heart block All of the patients had a moderate to severe M A S syndrome The prognosis in high grade A V block is usually considered to be poor Two of the 8 patients (25 per cent) died in the hospital and 3 more died at home within 1 year after discharge for a total mortality of 62.5 per cent in the group with advanced A V block Only 1 patient developed this heart block from digitalis which is a frequent cause of partial block

Summary

Several unusual forms of second-degree atrioventricular block associated with the Morgagni Adams Stokes (M A S) syndrome are discussed Three out of 100 patients with the M A S syndrome demonstrated a transient Mobitz Type II block Seven additional cases are reviewed from the literature All of the patients had frequently changing degrees of heart block and in only 1 patient did the Mobitz Type II block persist In all cases in which a clinical history is available Mobitz Type II block was associated with an Adams Stokes syndrome Although a particularly poor prognosis has been indicated for this type of block the outlook appeared to be no different from that in other cases of M A S syndrome in our series On the other hand Mobitz Type II block is of prognostic importance if it indicates that the M A S syndrome is likely to develop

Two patients who had 2 1 A V block with A V interference dissociation presented with the M A S syndrome Neither of these cases was caused by excessive administration of digitalis

Eight patients had advanced or high grade A V block related to their M A S syndrome All of them subsequently developed complete heart block Although odd numbered ratios of advanced heart block are said to be rare such forms were present in all 8 cases whereas 4 1 block was present in only 2 cases This may indicate that M A S syndrome is more likely to occur in the odd ratio type of advanced heart block

Awareness that these unusual forms of second-degree block are associated with M A S syndrome may enable the prediction of later development of complete heart block and M A S syndrome

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A simple technique for identifying P waves in complex arrhythmias

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It is difficult to determine precisely atrial activity in many complex arrhythmias. Atrial activity can usually be determined from the routine 12 lead electrocardiogram [illegible] special external chest leads. If the diagnosis is still in doubt, esophageal leads may be used. Esophageal electrocardiography was introduced in 1906[1] but it was not until 1936 that Brown popularized it. However, as late as 1962 a survey disclosed that esophageal electrocardiography is rarely used in most medical centers.[2] This may be due in part to inherent difficulties encountered in using the esophageal lead, such as the inability of the patient to cooperate and a wandering base line.

Intracardiac electrocardiography during cardiac catheterization has been used to help determine the location of the tip of the catheter and also in experimental work to advance knowledge concerning the electrophysiology of the heart. Recently, the platinum-electrode catheter has been employed for the detection of shunts, using hydrogen and ascorbic acid as indicators.[4] Experimental studies with a platinum tipped, Teflon coated wire† revealed that this flexible wire could be readily passed from a peripheral vein into the chambers of the right side of the heart without fluoroscopic aid.[5] It was considered feasible, therefore, to utilize this wire at the bedside in patients with difficult arrhythmias.

Technique. A median arm vein is selected which will accept an 18 gauge thin walled needle. The area is cleansed and draped. Under sterile conditions the needle is inserted into the vein, and the wire is advanced through the needle for a short distance. The needle is then removed so as to avoid any damage during manipulation of the wire. The electrocardiographic leads are attached to the patient's four extremities in the usual manner. At this point it is extremely important to make sure that *the recorder is properly grounded.*[6] The wire is then connected to the V lead terminal by means of an extension wire with alligator clips on each end (Fig. 1).

While the electrocardiogram is being monitored, the wire is advanced and generally proceeds to the right atrium without

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†The wire is stainless steel, size 0, and is coated with Teflon except for the ends. A piece of platinum [illegible] by .032 inches has been attached to one end and the other end of the wire has been left bare for connecting to an external lead. The wire is supplied in both 44-inch and 60-inch lengths. The wires used in this study were kindly supplied by Davis and Geck Division of American Cyanamid Co., Danbury, Conn.

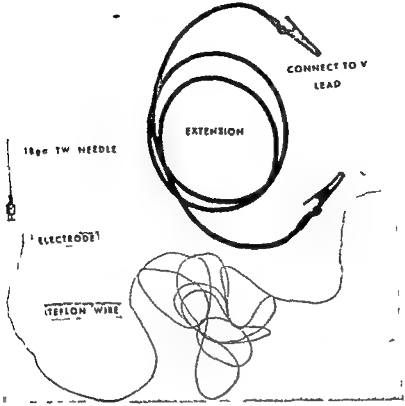

Fig *1* The apparatus See text

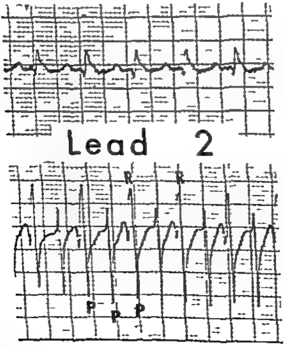

Fig *2* Atrial flutter with 2 1 block Standard Lead II fails to clearly identify atrial activity which is well shown with the intracardiac electrode (*bottom*) *R* QRS *P* Flutter waves

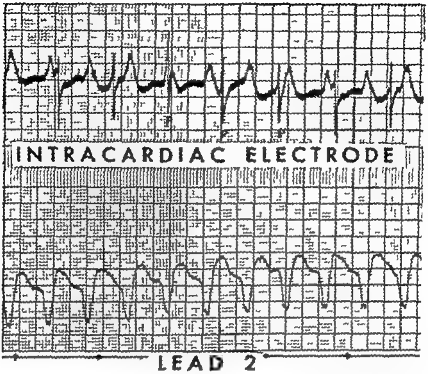

Fig 3 Ventricular tachycardia *Standard Lead II fails to clearly identify atrial* activity which is well shown with the intracardiac electrode which is positioned in the right atrium

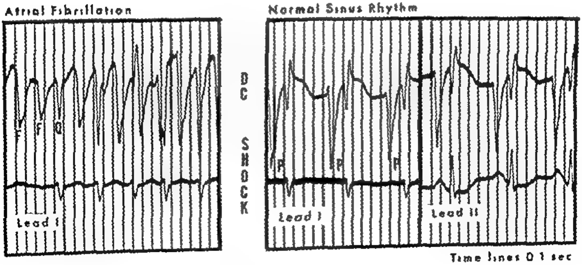

Fig 4 Simultaneous intracardiac electrocardiogram with platinum electrode wire in right atrium (*upper tracing*) and Standard Lead I in a patient with mitral stenosis Note prominent fibrillatory waves (*F*) in right atrium during atrial fibrillation With cardioversion normal *sinus rhythm* was restored and regular prominent P waves are clearly shown *Q* QRS complex

difficulty. As the electrode enters the right atrium, prominent P waves appear (Figs. 2 and 3). In the right atrium, the QRS complexes are relatively small and the P waves are very prominent, being as tall as 25 mm. Frequently, the wire will pass through the tricuspid valve into the right ventricle. When this happens, the P waves become smaller and the QRS complexes increase greatly in amplitude.

Comment. The above-described technique has been used in a number of patients with various arrhythmias, without a failure to advance the wire into the right atrium. In all patients it has been possible to determine atrial activity and its relationship to the QRS complexes without entering the right ventricle. Thus, except in the patient with atrial fibrillation, in whom entering the right ventricle may be necessary to clearly show that the Teflon wire is in the heart, the wire does not have to be advanced beyond the atrium. Caution must be exercised if the right ventricle is entered, because if sufficient wire is passed into the right ventricle, it may become knotted or tied about a papillary muscle or chordae.

Experience with this technique has demonstrated that only minimal cooperation of the patient is necessary, a stable base line can be achieved, and there is no trauma to the patient except for the discomfort of a simple venipuncture. The simplicity of this method has made it a useful clinical procedure for evaluating complex arrhythmias.

This Teflon-covered wire is also being used for the detection of left-to-right shunts with the hydrogen technique as a procedure in outpatients.

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Double ventricular parasystole

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Parasystolic rhythm is of special interest since this mechanism of ectopic impulse formation is different from that of other ectopic rhythms and is almost always indicative of organic heart disease,[1-4] although Pick[5] reported its occurrence in 3 young patients, aged 12, 13, and 25 years, of whom had no demonstrable heart disease. In another paper[3] observations in 10 cases of atrioventricular nodal parasystole were described, and in only 2 of them was there no heart disease. However, in a study by Scherf,[6] 2 out of 4 patients with atrioventricular nodal parasystole had diseased hearts.

Ventricular parasystole occurs more commonly than the supraventricular variety and correlates more closely with the presence of heart disease. In our experience at Barnes Hospital,[1,3] ventricular parasystole is encountered about once in every 900 routine electrocardiograms, which is much the same experience as that of others.[4] Scherf and associates[6,7] reported that ventricular parasystole has been estimated to occur once in every 1,200 electrocardiograms taken in a general hospital, whereas Katz and Pick[2] found 153 instances of parasystole in 100,000 electrocardiograms of 50,000 consecutive patients. The purpose of this paper will be to present 2 unusual cases of double ventricular parasystole which have been collected in the last few months at the Barnes Hospital Heart Station.

Case 1. A.W., a 58-year-old Negro man with a typical picture of generalized scleroderma, including cardiac involvement, died 2 weeks after admission to Barnes Hospital.

Case 2. C.H., a 51-year-old white man, was admitted to Barnes Hospital for repair of an interatrial septal defect which had been confirmed by cardiac catheterization. The chest roentgenogram revealed biventricular enlargement. Surgical repair of the defect was successful.

Analysis of electrocardiograms

In the first case, the routine electrocardiogram shows sinus rhythm with two types of ventricular ectopic beats with varying coupling intervals (Fig. 1). Lead II-a, II-b, and II-c are continuous strips, whereas Lead II-d is not. The upright QRS complexes of the ectopic beats (sixth, eleventh, thirteenth, fifteenth beats of Lead II-a; third, eighth, tenth, thirteenth beats of Lead II-b; second, fourth, seventh, ninth, fourteenth beats of Lead II-c; third

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fifth seventh beats of Lead II-d) will be designated Group A ventricular para systolic complexes for the purpose of this paper The downwardly directed ectopic ventricular beats (fourteenth beat of Lead II a first beat of Lead II c sixth eighth twelfth beats of Lead II d) will be referred to as Group B ventricular parasystolic beats The shortest interectopic intervals of the Group A complexes are relatively constant (between 108* and 126*) and the shortest interectopic intervals of Group B are also relatively constant (between 145* and 152*) The parasystolic cycles are measured either as the shortest interectopic interval or as the multiple of the shortest interectopic interval The parasystolic cycle lengths vary between 0 07 and 0 18 second a finding similar to that noted in our experience[1,3] and by others [4,8,13] There are frequent ventricular fusion beats in both groups which are quite characteristic of ventricular parasystole[1,3] In the mid portion of Lead II d conducted sinus beats have completely disappeared and instead the rhythm consists of bidirectional ventricular parasystolic tachycardia resulting from the combination of Group A and Group B *complexes* (*fifth* sixth seventh eighth beats of Lead II d) which occur at the rate of 90 per minute The Group A parasystolic pacemaker dominates that of the Group B beats mainly because of its faster rate although the possibility of intermittent parasystole can not be excluded The sinus rate is 87 per minute the Group A parasystolic rate is 53 per minute and the Group B parasystolic rate is 42 per minute An interesting observation is that the coupling intervals of some parasystolic complexes appear to be very short (0 36 to 0 38 second) which probably represents some degree of supernormality[11] The Group A parasystolic rhythm may be considered to be a slow ventricular parasystolic tachycardia because the rate (53 per minute) is faster than the inherent automaticity of impulse formation in the ventricles since as a rule the rate of an idioventricular rhythm is between 30 and 40 per minute[1]

In the second case the electrocardiogram consists of four strips of Lead II which are not continuous (Fig 2) The basic rhythm is atrial fibrillation alternating with runs of impure flutter and the ventricular rate is about 70 per minute There are two types of ventricular ectopic beats just as in the first case The lower voltage ectopic ventricular complexes (fifth eighth beats of Lead II A first third fifth tenth beats of Lead II B third eighth eleventh beats of Lead II C first third sixth ninth twelfth beats of Lead II D) will be designated as Group A complexes and are the dominant parasystolic beats because of their more

*These figures represent hundredths of a second throughout

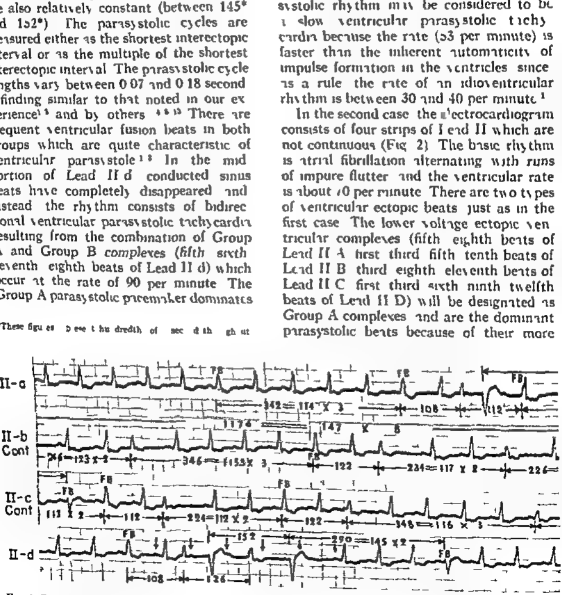

Fig 1 Case 1 Lead II a b and c are continuous strips Lead II d is not The tracing shows sinus rhythm with double ventricular parasystole Note two different ventricular ectopic QRS complexes (Groups A and B) There are frequent ventricular fusion beats (marked *FB*) The sinus rate is 87 per minute the Group A parasystolic rate is 53 per minute and the Group B parasystolic rate is 42 per minute

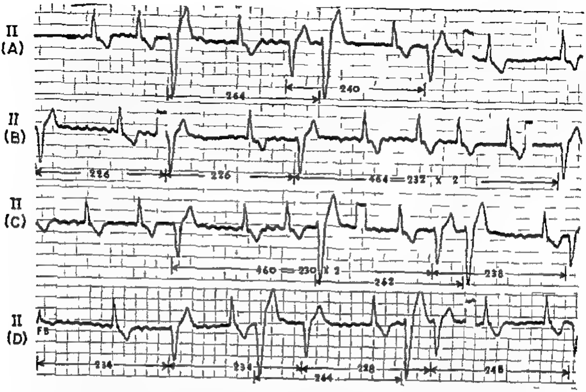

Fig 2 Case 2 The basic rhythm is atrial fibrillation with a ventricular rate of 70 per minute Note two different ventricular parasystolic beats (Groups A and B) with different parasystolic cycles Group A is the dominant stolic rhythm mainly because it has a faster rate than the Group B rhythm There is a ventricular fusion beat (marked *FB*) in Lead II D The para ystolic rate is 27 per minute in Group A and 2? per minute in Group B

rapid rate The other ectopic QRS complexes (third sixth beats of Lead II A sixth ninth beats of Lead II C fifth eighth beats of Lead II D) will be referred to as Group B complexes There is a ventricular fusion beat in Lead II D There are varying coupling intervals with relatively constant parasystolic cycles The shortest interectopic intervals of the Group A beats are between 226* and 248* and between 262* and 264* in the Group B complexes The variation of the parasystolic cycles ranges between 0 02 and 0 22 second The rate of the Group A parasystolic rhythm is approximately 27 per minute and that of Group B is about 22 per minute These rates appear to be too slow for an idioventricular rhythm Ventricular parasystolic rates may range between 20 and 400 per minute[1 2 11] The rapidity of discharge of the parasystolic impulse is considered to be outside the limits of physiologic automaticity of the usual impulse formation that is to say the supraventricular parasystolic rhythm is slower[3 8 9] and the ventricular form is faster[9] than would be expected However Scherf[16] in an experimental study with animals reported that the rate of ventricular parasystole does parallel in general the rate of the basic rhythm Nevertheless the slow parasystolic rates in Fig 2 in both Groups A and B and the marked variation in interectopic intervals raise the interesting question whether 2 1 or 3 1 exit block exists in the parasystolic rhythms although this cannot be proved

*These figures represent hundredths of a sec d through t

Comment

Double ventricular parasystole in patients (without an implanted artificial pacemaker) is a unique electrocardiographic finding The 2 cases presented in this paper may perhaps represent the first reported examples of double ventricular parasystole as far as can be ascertained from the literature It is possible that similar cases have been encountered

over the years which have not been recognized as examples of this arrhythmia

Parasystole has been reported by many clinicians[1-22] and several examples of artificial pacemaker induced parasystolic rhythms have been published by different authors[17,18]. Harris and associates[17] reported a case of what was thought to be a pacemaker induced paroxysmal ventricular tachycardia which resulted from malfunction of a self-contained long term internal artificial pacemaker and which developed after 16 months of uneventful performance by the pacemaker. In actuality, Figure 6 of their report shows an example of double ventricular parasystole resulting from the combination of artificial internal and external pacemakers; their case resembles electrocardiographically the cases presented in this paper with the exception that our 2 cases had spontaneous double ventricular parasystole. Clinically, the patients reported on here are both males with serious heart disease and cardiomegaly. One of them had generalized scleroderma.

Summary

Two cases of intermittent double ventricular parasystole have been described in detail. Although double parasystolic rhythms due to artificial pacemakers have been reported by others, this is perhaps the first report of spontaneous double ventricular parasystole. As stated previously, it is quite possible that similar electrocardiograms have been seen over the years but have not been recognized as examples of this arrhythmia. Both patients in this report were males and had serious heart disease; one had generalized scleroderma. It is premature to judge whether the occurrence of double ventricular parasystole is associated with a worse prognosis than is the occurrence of single parasystole.

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Electrocardiographic modifications in anemia

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The effects of anemia on the heart as judged by the electrocardiogram have been investigated by several authors with variable results; whereas some have failed to find significant alterations,[7] others have reported various changes according to the degree of hypoxia,[1-8] especially in the repolarization process. Stimulated by the existing disagreement, we undertook a study of the electrocardiographic patterns in a group of anemic patients.

Material and methods

The clinical material consisted of 100 patients with chronic anemia (hemoglobin levels below 8 Gm. per 100 ml.) who had been admitted to our Hospital between 1947 and 1961 and in whom electrocardiographic studies had been made prior to treatment. In 30 of these patients the electrocardiograms were taken at intervals throughout the therapeutic period.

The distribution of patients according to the type and degree of anemia is presented in Table I. In age the patients ranged between 11 and 88 years, with a mean of 45 years. The cases of normochromic normocytic anemia were of varied etiology: 23 cases of bone marrow hypoplasia ("refractory anemia"), 5 cases of hemolytic anemia, 2 cases of sideroblastic anemia, 3 cases of multiple myeloma, and 4 miscellaneous types.

In those patients studied serially, an electrocardiogram was repeated each week during therapy, which consisted of orally or parenterally administered iron, vitamin B_{12} given intramuscularly, or blood transfusions, depending on the type of anemia. Two patients with normochromic normocytic anemia due to refractory anemia and 2 others with megaloblastic anemia received therapeutic doses of iron orally or parenterally in addition to the adequate antianemic therapy.

Results

The electrocardiogram was normal in 81 patients and abnormal in 19. Eight of those with an abnormal ECG had an associated cardiopathy or hypokalemia, and the ECG did not show any changes in the repolarization process attributable to the anemia. The other 11 patients (Table II) showed ECG alterations of the hypoxic type probably secondary to the anemia. Of the latter group, in the patients studied serially the ECG alterations disappeared or improved as the hemoglobin levels increased.

Hypoxic alterations in the ECG in young patients occurred only when associated with extremely low levels of hemoglobin (2.7 and 3.5 Gm.) (Table II).

Autopsy was performed on 20 of the patients (Table III). Definite coronary

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pathology was found in 3 who had shown an abnormal ECG. In the others with a normal ECG the coronaries were free from pathologic changes except in one in whom mild atheromatous plaques were present although the vessels were patent.

The 12 patients with iron deficiency anemia who were studied serially developed a peculiar ECG change within a week after therapy was started; this change consisted of peaked, high-voltage T waves (Figs. 1 and 2). The alteration was evident mainly

Table I. Distribution of cases according to type and intensity of the anemia

Type	*Number of cases*	*Hemoglobin (Gm. per 100 ml.)*		
		Less than 4	*4.0–6.0*	*6.1–7.9*
Hypochromic	43	13	19	11
Macrocytic megaloblastic	13	0	[illegible]	6
Normocytic normochromic	44	6	22	16
Total	100	19	48	33

Table II. Patients with ECG alterations of the hypoxic type

Case number	*Age (yr.)*	*Hemoglobin (Gm.)*	*ECG alteration*	*Diagnosis*	*Comment*
1	19	7.7	Slight S-T depression. With iron therapy it disappeared and T became peaked	Iron-deficiency anemia	No evidence of intrinsic heart disease
2	25	3.5	T slightly negative in [illegible], isoelectric in [illegible]. QT +0.06	Iron-deficiency anemia	No evidence of intrinsic heart disease
3	37	[illegible] 7	Isoelectric T in D[illegible]. S-T depression in D[illegible] D[illegible], [illegible] and [illegible]. Negative T in [illegible]	Normocytic normochromic anemia	No evidence of intrinsic heart disease
4	38	6.2	Slight S-T depression. With iron therapy it disappeared and T became peaked	Iron-deficiency anemia	No evidence of intrinsic heart disease
5	45	7.3	Low voltage T in all leads. Improvement with therapy	Normocytic normochromic anemia	Diabetes mellitus
6	46	4.2	Low voltage T in all leads. Improvement with therapy	Normocytic normochromic anemia	Diabetes mellitus
7	51	5.3	Negative T in [illegible]	Normocytic normochromic anemia	Autopsy: calcified aortic atheroma and atheromas in coronaries. Fibrotic myocardial arteries
[illegible]	60	6.8	Low voltage T in all leads	Normocytic normochromic anemia	Essential hypertension. Aortic atheroma Grade III
9	63	5	S-T depression in D[illegible] D[illegible] and [illegible]. Negative T in [illegible] and [illegible] and isoelectric in [illegible]	Macrocytic megaloblastic anemia	Pulmonary emphysema
10	6[illegible]	6.9	S-T depression in D[illegible] D[illegible] [illegible] [illegible] and [illegible]. Negative T in [illegible] [illegible] and [illegible]	Macrocytic megaloblastic anemia	Pulmonary emphysema. Peripheral arteriosclerosis. Moderate essential hypertension
11	74	5.8	Negative T in [illegible] and [illegible]	Macrocytic megaloblastic anemia	Pulmonary emphysema. Aortic sclerosis Grade III

Table III Correlation between ECG pattern and anatomic state of coronaries and myocardium

Age (yr)	Hemoglobin (Gm /100 ml)*	Principal diagnosis	ECG pattern	Coronary arteries	Heart and aorta
11	4 5	Iron deficiency	Normal	Healthy	Healthy
16	5 0	Refractory anemia	Normal	Healthy	Atheroma in thoracoabdominal aorta
22	5 0	Refractory anemia	Normal	Healthy	Healthy
22	5 2	Lupus erythematosus disseminated	Normal	Healthy	Healthy
26	6 7	Iron deficiency	Normal	Healthy	Aortic atheroma Grade I
27	2 6	Iron deficiency	Normal	Healthy	Cysticercosis of the myocardium
37	6 4	Lupus erythematous disseminated	Normal	Healthy	Healthy
38	6 6	Hemolytic anemia	Normal	Healthy	Healthy
38	3 4	Refractory anemia	Normal	Healthy	Healthy
40	4 1	Refractory anemia	Normal	Healthy	Aortic atheroma Grade I
47	6 4	Iron deficiency	Normal	Healthy	Healthy
46	4 5	Iron deficiency	Normal	Healthy	Healthy
46	3 4	Acute leukemia	Normal	Healthy	Healthy
48	7 7	Pernicious anemia	Normal	Healthy	Healthy
51†	5 3	Hodgkin s lymphoma	Negative T in V_1	Atheromatous Fibrotic myocardial arteries	Calcified aortic atheroma
60	4 7	Refractory anemia	Normal	Healthy	Aortic atheroma
63	3 1	Refractory anemia	Q T +0 08 Right branch block	Permeable but tortuous and sclerotic	Persistence of the arterial canal Aortic atheroma
64	5 3	Iron deficiency	Normal	Healthy	Aortic atheroma
64	5 0	Refractory anemia	Normal	Permeable but with mild atheromatous plaque	Calcified plaques in aorta
68	6 1	Hodgkin s lymphoma	Low voltage and furring of QRS	Permeable but with moderate sclerosis and thickened arterioles	Moderate cardiosclerosis

*Determinations of hemoglobin were performed at same time that the ECG was recorded
†Case 7 in Table II

in the standard and left precordial leads appearing concomitantly with the therapeutic reticulocytosis and in some it persisted after the hemoglobin reached a normal level Neither hyperkalemia nor hypokalemia was observed in any of these patients The ECG abnormality was independent of the level of serum iron being observed equally in patients with high levels secondary to parenteral iron therapy and in those with low levels who were receiving iron orally On the other hand no modification in the ECG tracing was observed in 2 patients with megaloblastic and 2 with refractory anemia who received similar parenteral or oral doses of iron along with specific therapy (Fig. 3)

The P R values before and after therapy were compared in 14 cases the results did not show a constant pattern for the values increased in 9 and decreased in 5 cases

Discussion

In spite of the fact that the myocardium is very sensitive to hypoxia this study failed to demonstrate the occurrence of a constant pattern of electrocardiographic alterations in cases of chronic anemia Alterations were observed only occasionally and in a mild degree which indicates the efficiency of the compensatory mechanism of the body Of these, the circulatory ones are the most important and exert their action by increasing the circulatory speed and the cardiac flow and lowering the peripheral vascular resistance Stewart and associates[11] and Brannon and associates[1] have shown that in anemia the volume per

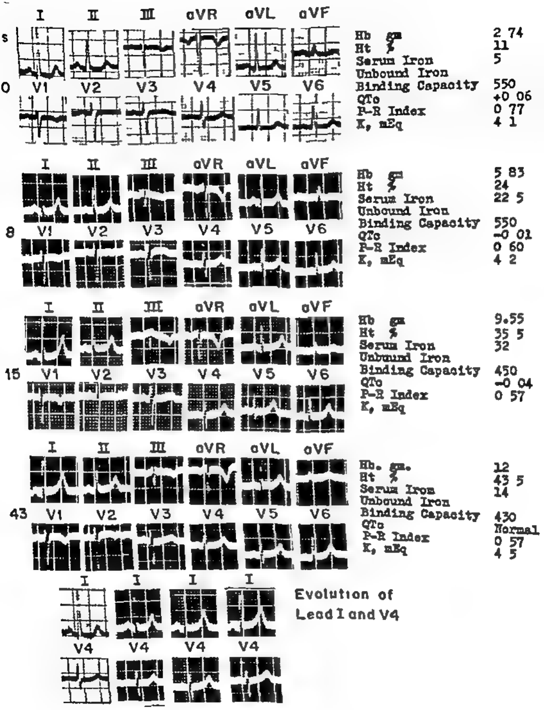

Fig *1* Nineteen year-old woman with iron-deficiency anemia Oral therapy with 0 9 Gm of ferrous sulfate daily started on day 0

minute the systolic volume the cardiac rate and the circulatory velocity are increased the peripheral resistance is lowered secondary to vasodilatation and reduced blood viscosity The latter authors[1] measured the cardiac flow in patients with various degrees of anemia and found that it increased in relation to the severity

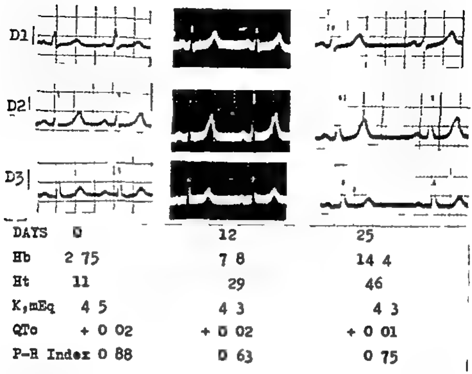

Fig 2 Thirty one year old man with iron deficiency anemia Daily injections of 100 mg of iron dextran were given on days 0 through 15

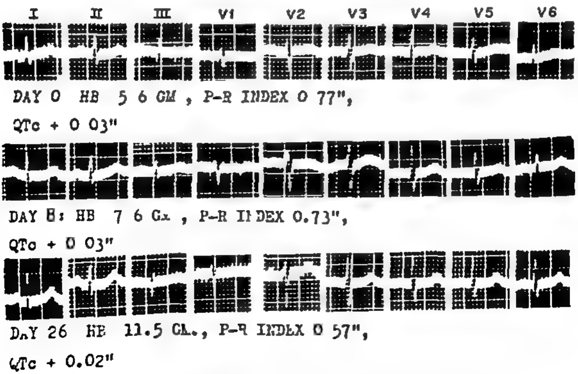

Fig 3 Seventy two-year-old woman with macrocytic megaloblastic anemia under treatment with vitamin B_{12}. Oral ferrous sulfate 0 9 Gm daily was given on days 8 through 10

the anemia reaching outputs of twice the normal when the levels of hemoglobin fell below 5 Gm per 100 ml in these conditions the peripheral resistance was lowered and the pulse frequency was increased Both groups of authors have pointed out that the decrease in the peripheral resistance explains why the ventricular work is not increased in anemia since the cardiac work is the product of volume per minute times peripheral resistance

Specific studies on the coronary arterial circulation in anemic dogs by Case and associates[18] have demonstrated that the coronary flow is amply increased in direct relation to the degree of the anemia They found that this increase in flow was due to a diminished coronary resistance plus a lowered blood viscosity depression of the ventricular function did not occur until the anemia was extreme They observed that in extreme degrees of anemia the depression of the ventricular function became manifest when the coronary arteries were maximally dilatated unable to further compensate On the other hand in the presence of experimentally produced coronary stenosis anemia rapidly precipitated the depression of ventricular function Results of our studies likewise showed that in the absence of coronary pathology signs of myocardial hypoxia appear only with extreme degrees of anemia (Table II)

The observation that the T wave alters during the recuperation phase in iron deficiency anemia has not been reported previously and it constitutes an interesting finding of the present work This alteration is similar to that seen in hyperkalemia subendocardial ischemia and diastolic overloading However in our cases the levels of serum K remained within normal limits and the other two possibilities can also be ruled out since the change was not seen during the control study when the anemia was most marked and it occurred only in the iron deficiency type of anemia

It is unlikely that the T wave alteration was due to the entrance of iron into the tissues since oral and parenteral administration of it to patients with megaloblastic and aplastic anemia failed to produce the abnormality Likewise the levels of serum iron bore no relationship to the electrocardiographic change

In iron deficiency states there is a lowered myoglobin content in both the striated and smooth muscles and a hypoconcentration of succinic dehydrogenase in the heart[9,10] Iron therapy in such cases causes an elevation of the myoglobin and iron enzymes Thus it appears likely that the biochemical processes which occur during the phase of rapid formation of myoglobin and enzymes are related to the aforementioned T wave alterations

Summary

Results of electrocardiographic studies in 100 patients with severe anemia (less than 8 Gm of hemoglobin) of various etiologies are reported Thirty of them were studied serially during therapy

Hypoxic electrocardiographic changes were observed in 11 patients these changes were seen to improve or disappear with the treatment in those patients who were studied at intervals throughout the course of therapy

The appearance of a peculiar electrocardiographic alteration during iron therapy in patients with iron-deficiency anemia is reported and its significance is discussed

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The natural history of idiopathic cardiomegaly

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The entity of idiopathic hypertrophy of the heart has aroused increasing interest in recent years and much speculation has arisen with regard to its etiology. Many factors have been suggested, but whether this is essentially a congenital defect or whether it is an acquired disease has never been clearly established since little is known about the state of these hearts prior to overt heart failure. The majority of reports and reviews on the subject are vague as to the onset of cardiomegaly, primarily because this specific information is difficult to obtain. Since this knowledge, that is, whether these patients had always had cardiomegaly or whether they acquired it later in life, appears to be an important void in our understanding of this condition, an attempt was made to investigate it.

Cases studied at a Veterans Administration Hospital are ideally suited for this purpose because all patients, in order to qualify for admission to a Veterans Administration institution, must at one time or another have successfully passed an Armed Forces Physical Examination; thus previous health records, including data concerning chest x-ray films, are available. The purpose of this communication, therefore, is to establish some evidence in regard to the natural history of idiopathic hypertrophy of the heart prior to the onset of overt heart failure. No attempt is made to review the clinical course of this condition after the onset of symptomatic heart disease, since this has already been done in a number of excellent and detailed publications.[1-3]

Only autopsy-proved cases were included in this series and specifically only those in which the total heart weight was over 500 grams and in which there was no evidence of coronary artery disease or abnormality, myocardial fibrosis or infarction, or valvular alteration. Similarly, a history of significant or permanent hypertension, rheumatic and other carditis caused exclusion. Cases which at autopsy showed extensive endocardial fibrosis, thus suggesting the diagnosis of fibroelastosis, were also eliminated from the series. As a result of this rather strict selection, only 11 cases were admitted to this study from an autopsy experience of 10 years at the Veterans Administration Hospital, East Orange, New Jersey.

After review of the autopsy and clinical findings, the Veterans Administration claims folders of these patients were studied. These included in all instances the original induction and discharge physical examinations as well as a statement in regard to the chest x-ray films taken at those times. Unfortunately, the actual x-ray films were not available in enough

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Table I

Name	Age	Race	Heart size on x ray film and blood pressure (mm Hg) — Induction	Discharge	First knowledge of enlarged heart
A S	65	W	July 22 1917 Negative physical exam	Jan 18 1919 Negative physical exam	1941
F W	51	W	Nov 28 1940 Neg 130/80	Oct 16 1945 Neg 170/80	?
C B	35	W	Dec 4 1945 Neg 120/80	Oct 9 1946 Neg 172/80	?
R S	43	N	June 18 1941 Neg 116/80	Nov 21 1945 Neg 110/80	1956
J G	34	W	July 8 1942 Neg 130/70	Dec 11 1945 Negative	1949
F P	46	W	June 3 1943 Neg 130/80	Feb 11 1946 Neg 122/70	?
W S	47	N	May 23 1944 Neg 120/60	Aug 16 1946 Neg 128/70	X ray 1953 Normal heart
A R	41	N	April 6 1943 Neg 136/84	June 26 1943	?
J B	63	N	Feb 23 1918 Negative physical exam	June 14 1919 Negative physical exam	1947
H S	52	W	Sept 23 1942 Negative	Sept 13 1945 Neg 120/84	?
W K	49	W	May 21 1942 Neg 148/88	Jan 9 1946 Neg 142/70	1958

cases although efforts to procure them continue Nothing is available with regard to the radiographic appearance of the chest in the veterans of World War I since radiographic examination of the chest was not part of the medical routine at the time The service medical records were studied which included documentation of all official medical contacts the patients had had while in Service From this it was apparent that all were healthy and vigorous men at the time of their military duties

The findings are summarized in Table I

It can be seen that the 9 veterans of World War II all had normal sized hearts without discernible hypertensive or cardiac abnormality both at the time of induction and at the time of discharge from Service One patient (J G) had been rejected by the Navy in 1942 because of a murmur but subsequent examination at the time of induction into the Army later that year and on discharge in 1945 failed to demonstrate cardiac hypertrophy Two patients had undergone antisyphilitic therapy while in Service but their serologic tests for syphilis were negative at the time of their discharge as well as during their terminal illness in the hospital and autopsy failed to demonstrate any syphilitic stigmata

Thus in these patients who were between 34 and 52 years of age at the time of death there was evidence of a normal sized heart and absence of hypertension or significant valvular disease 7 to 17 years prior to the onset of overt congestive failure In one patient in whom the diagnosis of hypertrophy of the heart was made prior to the onset of symptoms the time interval between the first documented evidence of a normal sized heart and diagnosis was 4 years The 2 veterans of World War I lived for 22 and 28 years respectively after their release from military service before the diagnosis of cardiac enlargement was made One of these patients was subsequently asymptomatic from a cardiac point of view for 12 years whereas the other developed congestive heart failure shortly after the cardiac diagnosis was made

Onset of heart failure	Date of death	Heart weight (Gm.)	Comment
1953	March 2, 1960	600	
November 1959	March 8, 1960	600	
January 1960	July 31, 1960	720	Sister had cardiomegaly
1956	April 14, 1958	710	Syphilis treated with Mapharsen. Kahn test negative
1956	July 17, 1957	800	Murmur heard 1942 by Navy
1959	Feb. 9, 1960	600	
1960	July 9, 1962	820	Syphilis treated. Serology negative
November 1955	Sept. 25, 1956	530	Discharged because of nonsuppurative arthritis, chronic, of both feet. Weight 248 lb.
1947	Sept. 21, 1955	610	
January 1962	March 18, 1963	710	
1958	April 7, 1963	750	

As mentioned earlier, a review of the literature of idiopathic cardiomegaly is not rewarding with regard to the question posed at the onset of this paper. Is this condition a congenital abnormality or is it an acquired disease? Specifically, there is a scarcity of documented instances of normal sized hearts prior to the diagnosis of cardiomegaly and subsequent clinical heart failure. Only two reports have been found in which definitive statements are made with regard to the finding of normal sized hearts. These include the case described by Simkins[4] of a 34 year old man who 2 years prior to death in congestive heart failure had a normal heart on a thorough physical examination. A study made by Norris[5] at the Philadelphia Naval Hospital contained the cases of 4 servicemen with idiopathic cardiomegaly—2 of these were inducted 2 and 1 years, respectively, before death and must be presumed to have had negative chest x-ray films at that time. As for the other 2 men, positive statements were made in regard to a normal sized heart on chest x-ray examination 10 and 14 months, respectively, prior to death in congestive heart failure. Autopsy in these cases showed cardiomegaly of the variety under discussion. Three reports from other Veterans Administration Hospitals (Serbin,[6] Spodick,[1] and Dye[3]) are available, but these fail to make positive mention of previous negative cardiac findings. Again, the nature of the subjects studied in these series, all of whom were ex-servicemen, suggests that their hearts were at least not grossly abnormal at some time in the not too distant past.

It is suggested, therefore, both from the cases studied personally and from the evidence available in the literature, that patients with idiopathic cardiomegaly had normal sized hearts at least 7 to 17 years prior to the onset of congestive failure. The conclusion, therefore, is that idiopathic cardiomegaly is an acquired disease.

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Changes in the levels of serum cholesterol and beta lipoprotein according to age, sex, and the existence of coronary heart disease

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The significance of the levels of serum cholesterol and lipoprotein in atherogenesis has been the subject of several controversies[1-5]

However epidemiological studies accumulated during recent years have favored the existence of some relationship between disturbances in lipid metabolism and atherosclerosis[6-8] On the other hand the influence of age and sex upon the levels of serum beta lipoprotein and cholesterol has been largely documented[9-11]

Other factors such as diet diabetes and stress which may also play a role in the concentration of lipids and lipoproteins in the blood will not be considered here

In Brazil only a few works have been carried out on this matter[12-14] so that up until now not enough data have been available to establish values for our apparently normal population

This paper represents the product of a survey undertaken with the chief aim of determining the levels of serum beta lipoprotein and those of cholesterol in the lipoprotein fractions in subjects of both sexes at different ages with and without coronary heart disease (most probably due to atherosclerosis)

Material

Two hundred and ninety two apparently normal individuals and 156 patients with coronary heart disease were selected for this study All subjects were chosen at random regardless of social level race or profession The majority of young normal subjects were selected from among high school and medical students Some were workers from the docks of Rio de Janeiro and a few were male and female nurses of a state hospital Our subjects cannot by any means be considered to represent Brazilians as a whole but we believe that they can be regarded as a fair sample of the population of Rio de Janeiro (State of Guanabara)

The patients with coronary heart disease were selected from private practice (38 men and 31 women) and the Outpatient Department of Santa Casa Hospital (54 men and 33 women)

The diagnosis of coronary heart disease was made on clinical grounds (evidence of angina pectoris and myocardial infarction) and on the existence of electrocardiographic changes (evidence of ischemia injury or necrosis at rest or after Master s exercise tolerance test[15]) Angina pectoris

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was present in 28 men and in 35 women. Forty men and 21 women had a past history and electrocardiographic evidence of old myocardial infarctions. In all patients with angina the electrocardiogram showed evidence of coronary insufficiency either at rest or after the exercise tolerance test. All the other individuals of this group who did not have angina or myocardial infarction displayed undisputed changes of diminished coronary flow in their electrocardiographic tracings (at rest or after the exercise test).

We wish to stress here that we have considered as normal only those individuals who did not show any clinical or electrocardiographic evidence of coronary insufficiency nor any physical or radiologic evidence of aortic involvement. Besides, we ruled out of the normal group all subjects who presented with any disease which seemed to favor or to be associated with atherosclerotic coronary heart disease such as diabetes, arterial hypertension, nephrosis, myxedema, cerebral and peripheral vascular insufficiency, and xanthomatosis.

Table I shows the distribution of the individuals according to age, sex, and the existence of coronary heart disease.

Methods

Beta lipoprotein was determined by a modification of Burstein's flocculation method.[16] Cholesterol in both alpha and beta lipoproteins was measured according to Abell[17] by means of a technique modified from Burstein's original method.[16]

1. Beta lipoprotein flocculation. In a test tube to 1 ml. of a 10 per cent solution of NaCl, 0.2 ml. of serum was added. 2 ml. of a 25 per cent solution of polyvinyl pyrrolidone (P.V.P.) was then slowly dropped into the tube. After this had been shaken several times, the mixture became cloudy. Thirty minutes later the sample was read at 700 μ in a spectrophotometer previously zeroed with a blank (pure serum). The number of optical density units of the sample was proportional to the amount of beta lipoprotein. This method was previously applied to 12 samples of serum in which the concentration of beta lipoprotein (in milligrams per 100 ml.) had also been determined by analytical ultracentrifuge. In this way we built a curve to allow the conversion of optical density units into milligrams per 100 ml., and our results will be expressed as such (Fig. 1). In cases of milky sera the chylomicrons were eliminated by centrifuge at 6,000 revolutions per minute for 15 minutes before zeroing the spectrophotometer and measuring the turbidity.

2. Measurement of cholesterol in alpha and beta lipoproteins. In a test tube 0.5 ml. of a 25 per cent solution of polyvinyl pyrrolidone (P.V.P.) was added to 1 ml.

Table I. Distribution of individuals according to age, sex, and the existence of coronary disease

Age group (yr.)	Normal		Coronary	
	Male	Female	Male	Female
Under 31	52	40	5	2
31-40	40	32	25	10
41-50	34	25	23	14
51-60	26	18	20	17
Over 60	15	10	19	21

Table II. Correlation between total cholesterol obtained by direct determination and by the sum of alpha and beta lipoproteins cholesterol (mg./100 ml.)

Case	Alpha	Beta	Alpha + Beta	Total cholesterol	Difference
1	63	214	277	288	11
2	54	176	230	250	20
3	57	194	251	260	9
4	75	252	327	338	11
5	68	227	295	304	9
6	64	216	280	287	7
7	54	198	252	258	6
8	78	195	273	289	16
9	62	198	260	274	14
10	53	164	217	221	4
11	50	118	168	174	6
12	67	210	277	285	8
13	72	247	319	334	15
14	57	156	213	224	11
15	54	229	283	292	9
16	66	245	311	324	13
17	72	236	308	326	18
18	57	194	251	260	9
19	46	122	168	172	4
20	62	186	248	258	10

of serum. After the tube had been shaken several times, a precipitate appeared which contained beta lipoprotein and euglobulins. The tube was then placed in a refrigerator at 4°C. for 24 hours. After this period of time the solution was centrifuged at 6 000 revolutions per minute for 10 minutes. The mixture now displayed two perfectly separated parts: a precipitate and a supernatant. From an aliquot of this supernatant (containing alpha lipoprotein) the cholesterol content was measured by Abell's method.[17] All supernatant was then removed and the precipitate was diluted with 1 ml. of a 0 9 per cent solution of NaCl. To this mixture 0 5 ml. of a 25 per cent solution of P.V.P. was again added (to make sure that the precipitate was formed only by beta lipoprotein and euglobulins; any remaining alpha lipoprotein was therefore removed). This new sample, after again remaining in a refrigerator at 4°C for 24 hours, was once more centrifuged at 6 000 revolutions per minute for 10 minutes. The solution was then decanted off and the remaining precipitate was diluted with 1 ml. of a 0 9 per cent solution of NaCl. From an aliquot of this last mixture (containing beta lipoprotein) the cholesterol content was determined according to Abell.[17]

We also measured total serum cholesterol levels in 20 cases (by Abell's method). By comparing the values of total cholesterol obtained by direct determination and those resulting from the sum of alpha and beta lipoproteins cholesterol, we found that the differences never exceeded 20 mg. per 100 ml. This corresponds to a maximum error of 8 per cent, which can be regarded as statistically insignificant (Table II).

Both methods of beta lipoprotein flocculation and beta lipoprotein precipitation with cholesterol measurement have been found to give highly reproducible results.

Results were compared by means of Student's t test, and probabilities were calculated according to the tables of Fisher and Yates.[18]

Results

Fig. [illegible] shows the mean values of serum alpha and beta lipoprotein cholesterol according to sex and age. Those of beta lipoprotein are shown in Fig. 3.

Table III. Serum alpha lipoprotein cholesterol (mg. 100 ml.)

Age group (yr.)	Male		Female	
	Normal	Coronary	Normal	Coronary
Under 31	ı0 ± 10	36 ± 8	77 ± 11	60 ± 6
31–40	65 ± 8	54 6	2 ± 10	51 ± 5
41–50	[illegible] 8	30 ± 6	66 ± 9	4ı ± 5
51–60	54 6	48 ± 5	62 ± 8	45 ± 5
Over 60	53 ± 5	49 ± 5	67 ± 8	44 ± 4

Mean value ± standard deviation.
P values between normal and coronary are less than 0 01 for both sexes in all age groups.

Table IV. Serum beta lipoprotein cholesterol (mg. 100 ml.)

Age group (yr.)	Male		Female	
	Normal	Coronary	Normal	Coronary
Under 31	109 ± 27	240 ± 46	107 ± 20	218 ± 2ı
31–40	1ı0 ± 30	218 ± 47	115 ± 21	210 ± 25
41–50	192 ± 38	242 ± 39	134 ± 24	237 ± 35
51–60	188 ± 45	234 ± 35	138 ± 21	248 ± 44
Over 60	180 ± 40	277 ± 30	12ı ± 20	254 ± 42

Mean value ± standard deviation.
P values between normal and coronary are less than 0 01 for both sexes in all age groups.

Table V. Serum beta lipoprotein (mg. 100 ml.)

Age group (yr.)	Male		Female	
	Normal	Coronary	Normal	Coronary
Under 31	4ı0 ± 54	777 ± 73	437 ± 47	ı50 ± 68
31–40	644 ± 67	807 ± 78	4ı0 ± 66	ı98 ± 75
41–50	780 ± 60	8ı8 ± 8ı	587 ± 68	884 ± 83
51–60	7̄48 ± 54	8ı5 ± 83	678 ± 66	873 ± 87
Over 60	725 ± 51	812 ± 81	613 ± 58	836 ± 79

Mean value ± standard deviation.
P values between normal and coronary are less than 0 [illegible] both sexes in all age groups.

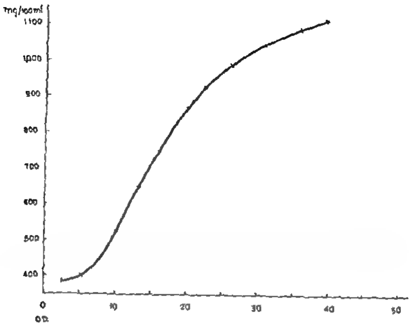

Fig 1 Curve for conversion of optical density (O D) units into milligrams per 100 milliliters (mg /100 ml) The O D units were determined by spectrophotometry and the mg /100 ml by analytical ultracentrifuge

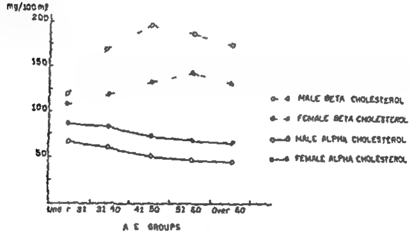

Fig 2 Mean values of serum alpha and beta lipoproteins cholesterol in apparently normal males and females in different age groups

In Tables III IV and V the mean values of serum alpha and beta lipoprotein cholesterol and beta lipoprotein found in normal individuals and in patients with coronary heart disease are compared

From the inspection of these figures and tables we may *ascertain the effects of age* and sex as well as the changes observed when there is evidence of coronary heart disease (and by inference atherosclerosis)

There is a trend toward a decrease in the levels of alpha cholesterol with age However the differences found among the several age groups are insignificant We may then consider that the cholesterol content of alpha lipoprotein remains for practical purposes unchanged throughout life (Fig 2)

Levels of serum beta lipoprotein and beta cholesterol increase up to 60 years of age reaching a maximum at the fifth decade among men and at the sixth decade among women (Figs 2 and 3) The differences between the mean values found

in the younger age group (under 31 years) and those in the older age groups (41 to 60 years) are for both beta lipoprotein and beta cholesterol statistically significant ($p < 0.01$)

Females display throughout life higher levels of serum alpha cholesterol than do males The difference between the sexes although statistically significant ($p < 0.01$) is not remarkable (Fig 2) As for serum beta lipoprotein and its cholesterol content we found no significant differences between the sexes under 31 years of age ($p = 0.1$) With increasing age however beta lipoprotein and beta cholesterol increase in the serum particularly among men and from the fourth decade onward the differences between men and women become highly significant ($p < 0.005$)

It was observed that in the presence of coronary heart disease the mean values of alpha cholesterol decreased whereas those of beta lipoprotein and beta cholesterol increased This was true for both sexes in all age groups The differences found between apparently normal and coronary subjects were statistically significant (Tables III IV and V) and more pronounced among women over 50 years of age

Discussion

Both epidemiological data and biochemical studies accumulated for many years constitute strong evidence in favor of the existence of some relationship between lipids lipoproteins and atherosclerosis Ancel Keys observations are too impressive to be overlooked [6] Data already collected from the Framinghan Study can by no means be disregarded [19]

On the other hand pathologists since Vogel [0] are in agreement upon the high content in lipids (cholesterol in particular) of the atheromatous plaques [II III]

Whether lipid infiltration into the arterial wall is a primary [24] or secondary [2] event in atherogenesis remains to be definitely established Either way the deposition of fat occurs in the early stages of atheromatous lesions [26] And where does this fat come from? Mostly from the blood since local lipid synthesis although it may occur [27 23] is not enough to account for the deposition of large amounts of fat

Lipids of course because of physico-chemical properties do not exist in the blood as such They are combined with special protein molecules forming the so called lipoproteins

Evidence now exists which indicates that beta lipoprotein is the one involved in the process of atherogenesis [9] This lipoprotein penetrates into the arterial wall and because of certain changes in the ground substance it becomes trapped and releases its lipid content mostly cholesterol and triglycerides [1]

Recent investigations have pointed out that the levels of beta cholesterol and beta lipoprotein show a better correlation with the incidence of atherosclerosis than do the levels of total serum cholesterol [30 31] The results we have obtained seem to substantiate most of the considerations referred to above

The levels of serum beta lipoprotein and beta cholesterol were definitely higher among patients with coronary heart disease than among apparently normal individuals whereas in so far as alpha cholesterol is concerned the opposite occurred And of course when we speak of coronary heart disease we mean (at least for the purpose of this paper) atherosclerosis

Some other of our findings also deserve to be stressed and discussed

1 Levels of serum beta lipoprotein showed a sharp elevation among apparently normal individuals in the 41 to 50 year age group Is it not an interesting coincidence that atherogenesis also seems to reach its maximum at this period of life?

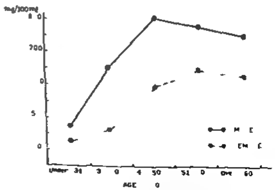

Fig 3 Mean value of serum beta lipoprotein in apparently normal male and females in different age groups

What electrocardiographic leads to take after exercise?

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Serious gaps exist in information about the most effective techniques for the recording and interpretation of electrocardiographic responses to exercise tests. However, exercise electrocardiography is a practical tool to apply and provides empirical data of great value in the diagnosis of heart disease and in the evaluation of cardiac functional status. It gives objective and semiquantitative evidence of inadequate myocardial perfusion. It is the only objective method susceptible of wide routine application for the detection of coronary artery disease prior to manifest clinical episodes and for "validating" a history of chest pain.

It was logical to employ exercise electrocardiographic tests in the epidemiological studies on coronary heart disease coordinated by this laboratory, both to increase the "yield"[1] of findings relevant, it was thought, to coronary disease and to establish the value of postexercise changes for predicting coronary disease and mortality. In these studies a systematic attempt is being made to answer some of the practical questions which persist about techniques and standards for the test.

One of these questions [redacted]: What electrocardiographic leads to take after exercise? Both recommendations and practice vary widely in this regard.

A partial answer may be provided by inspection of the distribution of "positive" S-T findings according to lead location in the postexercise electrocardiogram.

In this study, records were taken under the conditions of field examination of total populations of men who were 40 to 60 years of age. All 12 conventional leads were recorded nearly simultaneously (within a period of 15 seconds) on multichannel direct writing apparatus (Elema), starting 45 seconds after cessation of the effort, which was a standard 3 minute step test. Tracings at subsequent intervals were not taken routinely, but only when the electrocardiographer present noted suspicious changes in the immediate record. These distributions refer, therefore, to those cases in which an "early positive test" occurred. The question of optimal intervals of postexercise recording will be taken up in a later article. "Positive" diagnoses are based on a clinical classification of S-T segment depression in the electrocardiogram which was devised particularly for epidemiological comparisons[1] and they are detailed as follows:

Category 4. S-T junction and segment

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Table I *Frequency of S T depression after exercise according to ECG lead among 100 positive cases**

	I	II	aVL	aVF	V_1	V	V_3	V_4	V_5	V_6
Frequency and per cent of cases with S-T depression by lead	8	17	6	16	1	2	23	53	[illegible]	40
Frequency and per cent of cases with S-T depression only in a single lead		1		4			1		5	

*F m simulta eou multichan el recording f 12 leads with span of 15 seconds t 1 min t after exercise

(measured from preceding P R interval at onset of QRS) (1) S-T J depression of 1 mm or more in any of I II aVL aVF V_{1-6} (2) S-T J depression *of 0 5 to 0 9 mm and* S-T segment horizontal or downward sloping in any of I II aVL aVF V_{1-6} (3) No S-T J depression as much as 0 5 mm but S-T segment sloping downward and reaching 0 5 *mm or more below P R base line in* any of I II aVL aVF V_{1-6}

Results

In Table I the data on 100 successive cases *indicate* what is well known that most positives (89 per cent) are found from Lead V_5 This should not argue for the recording only of Lead V_5 The added effort of taking a complete electrocardiogram when the patient is already wired up is small compared to the total effort of these studies and the difference in yield of information However Table II indicates that information about S-T depression obtained *from Leads I* aVL V_1 and V is redundant and the recording of a block of six leads II aVF V_2 through V_6 probably provides all the information available from conventional electrocardiographic leads in this regard

This has practical importance since time may be an important variable in the detection of postexercise S T changes and the speedy efficiency of a block recording of these six leads on multichannel apparatus eliminates concern about it When four

Table II *Per cent of all positive cases of postexercise S T depression detected with recording of limited leads**

Leads	*Per cent detected*
V_5 alone	89
$V_{5,6}$	91
V 6	93
V_3 5 6	94
V 4 5 6	94
V 3 5 6	94
I V_3 5	94
II V_3 5	96
II aVL $V_{3\,4\,5\,6}$	96
II aVF V 4 5 6	100

*All ases were d tected by recording fter exercise the combi nati n of II aV V through V_6 (S-T depression in III and a aVR were gnored) F ndings are based n an bsolut J depressi n of 1 mm. or mor o 0.5 mm. plus scheme segment not upon a change relative t the resti g electrocardi gram

channel apparatus is used two blocks of four leads are made (1) $V_{3\,4\,5\,6}$ (2) I II aVL aVF When the slower technique involving single-channel apparatus is employed it is clear that after exercise the V leads should be recorded first in reverse order V_6 through V_2

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Conclusions

Late postexercise ECG records provide information in addition to that obtained immediately after exercise in that the maximum change sometimes occurs after several minutes but the yield (10 per cent) is not so high as is implied in the strong recommendations for repeated recording as a routine procedure Furthermore in only one instance out of 50 positive tests was there a significant change at 4 minutes (negative precordial T waves) in the *absence* of a change immediately after exercise Thus if tracings are made subsequent to the immediate record *only* in cases which have S T T findings immediately few true positives will be missed and important bias from selective application of repeat records to that limited portion of the whole is unlikely

These findings do not argue against the routine application in a heart clinic of postexercise ECG recording at several time intervals Indeed they indicate that if maximal S T T change is important or if ischemic type change is especially important or if the length of time that the S T T anomalies persist after stress is important one would do well to record more than one postexercise electrocardiogram But they also indicate that most immediate S T T findings (90 per cent) do not evolve significantly or they disappear from 3 to 5 minutes after effort Arrhythmias are found most frequently *during* exercise and are rarely seen at all on the postexercise electrocardiogram[3]

These findings justify the practice of recording only the immediate postexercise electrocardiogram (approximately 1 minute after the effort) in the heavy schedule of population studies but the practice presupposes an electrocardiographic judgment An electrocardiographer should be present to decide whether to take subsequent postexercise records in cases with findings at rest or immediately after exercise both to assess the clinical state of the subject and to collect the optimal information on ischemic changes

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Experimental and laboratory reports

The relation of age to the duration of contraction, ejection, and relaxation of the normal human heart

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The purposes of this report are (1) to determine the effect of normal aging on the duration of certain intervals of the cardiac cycle and (2) to obtain base line data over a broad age range from normal subjects as a means of comparison with various types of cardiac disease to be studied in the future

Sixty five healthy persons were studied All had normal hearts as judged by clinical and electrocardiographic criteria Their ages ranged from 9 to 97 years A few were accustomed to vigorous activity but most of them were of sedentary habits

Simultaneous electrocardiograms (Leads I and II) carotid pulse tracings and traces of absolute precordial movement (kinetocardiograms) were secured according to the previously described technique [1] All records were obtained with the subjects in the recumbent position with breathing suspended at the end of normal expiration

Attempts were made to measure the various intervals illustrated in Fig 1 Such measurements are reasonably accurate in the case of the relatively long periods elapsing between excitation and the onset of the carotid upstroke (Q CU) the duration of ejection as judged by the carotid upstroke to incisura (CU CIN) and the isometric relaxation phase as indicated by the time between the carotid incisura and the start of the precordial outward deflection signifying passive filling (CIN PF) The measurements of the brief pulse transmission times are attended by a much greater relative error

The determinations of electromechanical lag are difficult because the time interval is short and the separation of motions due to atrial relaxation from those due to the onset of ventricular contraction may be difficult or impossible Consequently these data as derived from the precordial motions are supplemented in Table I by measurements of the time of onset of the rise in ventricular pressure in a series of patients with cardiac disease who were subjected to catheterization

The duration of left ventricular iso

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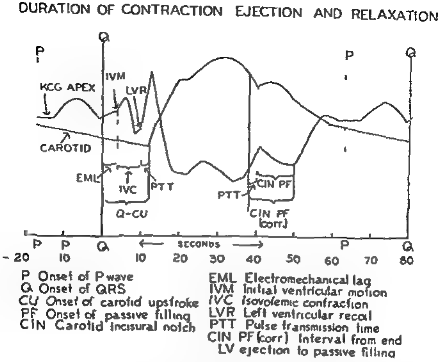

Fig. 1. The Q-CU time is composed of three intervals: (1) electromechanical lag, i.e., Q to onset of initial precordial deflection due to ventricular contraction; (2) isovolumic contraction period, i.e., start of contraction to ejection as indicated by left ventricular recoil; and (3) pulse transmission time, i.e., recoil to carotid upstroke. The carotid upstroke to incisural notch interval is a relatively good guide to the duration of ejection because the error due to pulse transmission time is apparently the same at the onset as at the end of ejection (see text). *The duration of isovolemic relaxation [CIN PF (CORR)]* may be obtained by adding PTT to the measured CIN PF interval. The sources of error in measurement and calculation are discussed in the text.

volumic contraction was estimated by the formula IVC = Q CU − (Pulse transmission time + 0.038 second). The reason that a value of 0.038 second is assumed for the electromechanical lag is indicated later. In any case, the estimated values for the duration of isovolumic contraction represent crude approximations.

It was not possible to measure each function in each subject because of occasional uncertainty concerning the time of onset of a given event. Therefore, the number of measurements varies somewhat in the different tables and figures.

For the sake of brevity, the complete data are presented only on those relationships which seem to be especially significant and have not been observed previously by others (Figs. 2, 4-7). Data which display less striking correlation or which represent confirmation of already reported findings are presented in summary only (Fig. 3).

Relationships which were studied but exhibited little or no correlation are mentioned in the text but are not illustrated in the figures.

Results

I. Interval from onset of excitation to start of carotid upstroke (Q CU). This tended to decrease with age (Fig. 2) and exhibited a minimal and irregular trend toward increased duration at slower heart rates. The several subdivisions of the Q CU period may now be considered (see Fig. 1).

A. PERIOD FROM THE START OF EJECTION TO BEGINNING OF CAROTID UPSTROKE (PULSE TRANSMISSION TIME). Since the pulse wave velocity is known[3] to increase markedly with age, neglect of this interval will cause a relatively large error in the estimation of the length of the period of isovolemic contraction. The time from the onset of left ventricular ejection, as indicated by

precordial recoil (LVR) to the start of the carotid upstroke is illustrated in Fig 3 A The linear shortening of the LVR CU time with advancing age is clearly shown

II PERIOD FROM ONSET OF EXCITATION TO BEGINNING OF LEFT VENTRICULAR CONTRACTION (ELECTROMECHANICAL LAG) An attempt was made to measure this interval i e the time from the onset of excitation to the first precordial motion which was thought to be related to ventricular activity The error of such measurements is large because of the small size of this motion and its confusion with terminal atrial activity Nevertheless the average values agreed well with the average time of onset of the rise in left ventricular pressure in a series of patients in whom the left ventricle had been catheterized (Table I) The average value of 0 038 second in the normal subjects agrees with previously published findings[4] No trend was found in relation to age or to length of cycle In attempting to estimate the duration of electromechanical lag in a given person it is probably less inaccurate to assume the average value for all normal subjects (0 038 second) than to try to measure this interval for the individual

C DURATION OF ISOVOLUMIC CONTRACTION This period which follows period B and precedes period A above cannot be measured directly by the techniques herein employed It cannot be measured accurately in man by utilizing the first heart sound because there is evidence[4] that the onset of ventricular contraction precedes the first sound by 0 04 second or more

Fig 3 B summarizes the data for the duration of isovolumic contraction as calculated by subtracting the sum of the left ventricle to carotid transmission time (as estimated from the age regression line in Fig 3 A) and the electromechanical lag (assumed to be 0 038 second) from the Q CU time Despite the wide scatter a trend toward a slight increase in duration of isovolumic contraction with advancing age is shown In adults this increase appeared to be relatively independent of heart rate (Table II)

Comment These findings explain the paradox of the shorter Q CU interval in older persons This appears to be due entirely to more rapid transmission of the pulse Assuming reasonable accuracy for the rough method that we have employed to measure the period of isovolumic contraction this interval is not shortened but is slightly longer in older persons

II Duration of ejection The simplest method of measuring this period is use of the carotid upstroke–to–carotid incisural notch (CU CIN) interval This increased markedly with longer cycle length (Fig 3 C) and slightly with age (Fig 3 D) The increment with age appeared to be entirely related to slower average heart rates in the older subjects Lombard and Cope found prolongation of CU CIN with increase in cycle length but inconsistent change with age Our data for CU CIN in relation to heart rate are similar to those of Lombard and Cope[5] and Weissler and associates[6]

The validity of the CU CIN interval as an index to the duration of ejection depends on the assumption that the time from the start of ejection to the onset of the carotid upstroke is equal to the time from the end of ejection to the carotid incisural notch This assumption has been supported by simultaneous measurements of the upstroke incisura interval in the central aortic pressure pulse and in the carotid displacement pulse

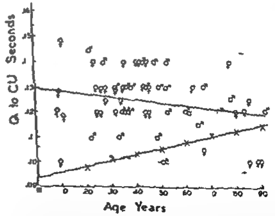

Fig 2 Excitation to-carotid upstroke interval in relation to age Despite wide scatter there is a trend toward a shorter excitation–carotid up troke (Q CU) interval with increasing age When the regression line is corrected by subtracting the average value for the subject s age for the pulse transmi ion time (from left entricle to carotid artery Fig 3 A) the trend is reversed (X X) The mean excitation to ejection time as so computed tend to increase lightly with ad ancing age r (central solid line) = 215 y = 13007 – 00013x Sy s – 017

III. Interval from end of ejection to beginning of filling. The onset of passive filling (PF) can usually be readily identified in traces of precordial motion (Fig. 1), although there is uncertainty whether the two ventricles always start to fill simultaneously. The duration of the interval between the carotid incisura and the start of filling increases strikingly with age (Figs. 4 and 5). Fig. 6 indicates prolongation of this period with increase in cycle length. However, this effect is small compared to the increase with advancing age (Fig. 7). The prolongation of the CIN-PF interval with age is therefore relatively independent of changes in heart rate.

Data already cited indicate that the end of the ejection-carotid incisura interval is shorter in older persons because of the decrease in pulse transmission time in them. When the measured values for the carotid incisura to passive filling periods were corrected for this factor, the data displayed in Fig. 8 were obtained. These indicate that the prolongation of the CIN-PF interval due only in small degree to alterations in lse wave velocity and that the duration left ventricular isovolumic relaxation increases by an average of about 40 per cent between the third and ninth decades.

Discussion

Except for the previously well-established shortening of pulse transmission time, the progressive prolongation of the period (whether or not corrected) between the carotid incisural notch and the onset of filling was the most striking change with advancing age.

It would be desirable to measure the duration of isovolumic relaxation in the normal human subject by more direct methods. Electrokymograms are so influenced by relaxational changes in shape as to be of limited value for this purpose. Study of pressure curves has led us to the conclusion that neither ventricular records nor atrial records will alone suffice. The pressure in the still relaxing ventricle may continue to decline after filling has begun. The early diastolic fall in atrial pressure curves may be due to diminished bulge of the closed atrioventricular leaflets as ventricular pressure declines, rather than to the onset of ventricular filling. For accurate detection of this event it is necessary to secure simultaneous equisensitive pressure curves from one atrium and from the corresponding ventricle and then note the time of crossing. Until such information on normal persons over a wide range of age is available, the technique herein employed, although indirect, appears to be the only one available. It is also entirely atraumatic.

Lengthening of the interval between the carotid incisura and the onset of filling could be due to an early incisura or to late filling. In older subjects the duration of ejection was not diminished (Fig. 3 *D*) and the incisura did not occur earlier than

Table I. The electromechanical lag (start of excitation to onset of contraction) as determined by precordial motions and by ventricular catheterization

Method	Subjects studied		Interval (sec.)		Remarks
	Clinical state	Number	Range	Mean	
KCG: Q to first ventricular motion	Normal	50	0.03-0.05	0.038	1. Large relative errors by both methods because: a. Artifacts; b. Brevity of interval; c. Initial ventricular deflections of ECG, KCG, and pressure curves may be gradual
Catheter: Q to onset of rise in pressure	Congenital or rheumatic heart disease*	RV 34	0.03-0.065	0.047	
		LV 12	0.02-0.05	0.034	2. Note good agreement between KCG and LV pressures

*Thirty-one of the 34 patients were Class I or II. QRS duration was normal (<0.11 sec.) in 32 patients.

Table II Duration of excitation ejection inter val and of calculated period of iso olumic contraction in relation to age and to cycle length in persons with normal hearts

Age group Mean and range (yr)	Number of subjects	Mean cycle length (sec)	Excitation to ejection* (sec) Mean values		Duration of isovolumic† contraction (sec) Mean	
			A Measured	B Calculated	Method I	Method II
9 8 (9 11)	5	0 72	0 08"	0 090	[illegible] 049	0 052
24 9 (22 28)	8	0 82	0 101	[illegible] 10"	0 066	0 067
35 3 (32 39)	14	0 87	0 106	0 101	0 068	0 063
44 7 (41-49)	[illegible]	0 86	0 112	0 112	0 074	0 074
59 3 (50 70)	11	0 92	0 106	0 10"	0 068	0 069
83 1 (73 97)	10	0 86	0 112	0 112	0 074	0 074

Durations elative to cycle lengtl in adults

Cycle range (sec)	Age range	Number of subjects	Mean values (sec)	
			Excitation to ejection	Iso olumic contraction
0 66–0 79	22–89	14	0 108	[illegible] 067
0 80–0 89	72–97	21	0 107	[illegible] 069
0 90–0 99	28–89	[illegible]	0 110	[illegible] 069
1 00–1 16	37–85	11	0 109	[illegible] 069

* Measured as nt rval f m nset of QRS t l ft ventn ul rec f n ea h subject
B C l lated by subtracti g rage p lse tra m n time for ge f m Q–car t d upst ke nt rval
† I A 0 038) 0 038 = M val f elect mecha cal lag f 50 ubjects.
II B 0 038)

in young persons Thus the long CIN PF interval was due to a diminished rate of ventricular relaxation The studies of A V Hill[7] indicate that in skeletal muscle relaxation (which is not the same as recovery) is a passive process dependent on elastic rebound when contraction ceases If the same is true of cardiac muscle then the older normal heart may be compared to a dead tennis ball which having been compressed many times has a diminished capacity to rebound Apparently not

the skin but also the heart tends to lose elasticity with the passage of years The possibility that factors other than diminished elasticity such as patchy areas of fibrosis or of fatty infiltration or changes in catechol content may be responsible for the slowing of relaxation cannot be excluded

The relaxation process actually begins before ejection ceases[8] and the terminal phase is still in progress after filling begins[9] Therefore the steady increase wit

vancing age in the CIA-PI interval indicates only a slowing of isovolumic relaxation, i.e., that portion of the process which occurs during the decline in ventricular pressure from aortic to atrial levels.

There is ample evidence that the rate of ventricular relaxation is a dynamic function and may be altered by mechanical or pharmacologic influences.[10,1] It has been proposed that such alterations are dependent on changes in the viscous elastic properties of the ventricles.[10] The effect of age in retarding relaxation is similar to that of drugs which depress ventricular contractility.[11] The prolongation of isovolumic relaxation in older persons may be related

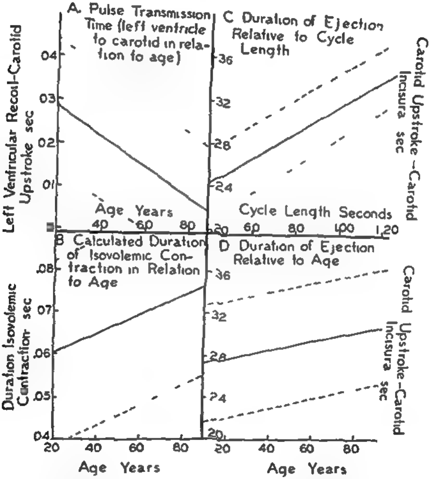

Fig. 3. The regression lines (*solid*) and the broken lines representing two standard deviations above and below are shown, the points from the individual subjects being omitted. *A* and *C*. The high correlation between age and pulse wave velocity (i.e., negative correlation between age and pulse transmission time) and between cycle length and duration of ejection are in agreement with reports by other observers (*see text for citations*). *B*. The duration of isovolemic contraction was calculated as follows: Q-CU time − [Electromechanical lag + pulse transmission time]. The average value for all normal subjects (0.038) was assumed for electromechanical lag (*see text*) and the average value for the subject's age (*A*, *solid line*) was assumed to be the pulse transmission time for the individual. Thus, the values for duration of isometric contraction represent crude approximations. However, the agreement of the slope with that of the values for Q-ejection (\ \ Fig. 2) suggests a general trend toward greater duration of isometric contraction with increasing age. *D*. The tendency toward prolongation of ejection with increasing age was slight and was apparently related to the lower average heart rate of the older persons (*see text*). *A*, $r = -.722$; *B*, $r = .423$; *C*, $r = .707$; *D*, $r = .316$.

to a common bedside observation. Ectopic tachycardia of a degree which is easily tolerated by young persons may precipitate congestive heart failure in elderly subjects even in the absence of clinical or electrocardiographic evidence of structural cardiac disease.

It is possible from the data to arrive at a rough estimate of the critical rate for old hearts. Thus at a rate of 120 the mean duration of ejection is about 0.25 second (Fig. 3 C). At age 70 the Q-left ventricular ejection interval, which is relatively independent of rate, is about 0.11 second (Fig. 2) and the mean duration of isovolumic relaxation is about 0.13 second. Thus the time from the onset of excitation to the beginning of passive filling would be 0.49 second, or only 0.01 second less than the cycle length. Assuming an interval of 0.05 second between the start of excitation and the elevation of ventricular pressure to a level above atrial pressure, we are left with a total period of 0.06 second available for ventricular filling. Despite the crudeness of the calculation, which neglects various modifying factors, we arrive at a value for the critical resting heart rate of older persons (120 per minute) which is in fair agreement with clinical experience.

Rough estimates of the duration of the periods of electromechanical lag and of isovolumic contraction (mean values for adults about 0.038 and 0.068 second, respectively) show that they are not markedly different from those which have been measured in dogs. Wiggers[14] reported evidence that the onset of the rise in ventricular pressure as recorded by his manometers was an accurate guide to the beginning of contraction. He mentioned intervals of 0.03 to 0.045 second after the start of excitation in dogs. Both in dogs and man (indirect estimate) an average value of 0.03 second for isovolumic contraction was found[9] at cycle lengths of 0.90 second. Our data indicate a somewhat longer interval in the human adult. The difference is possibly due to the utilization by Wiggers of the first heart sound as a guide to the start of contraction in man. Actually contraction begins about 0.015 second earlier.[4] Nevertheless our own measurements of this period are crude and indirect and can be considered to be only a rough approximation. Our assumption that the apparent

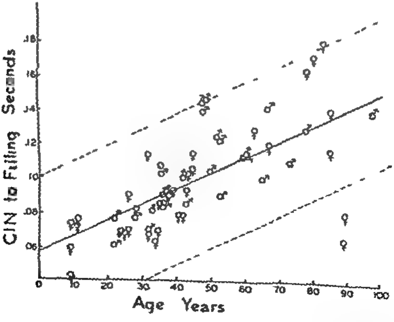

Fig. 4. Carotid incisural-passive filling interval in relation to age. A pronounced increase in the duration of the interval between the carotid incisural notch and the onset of passive filling is seen with advancing age (see also Fig. 8). $r = .69$. $y = 0.0567 + .00094x$; $\sigma_{y.x} = .02194$.

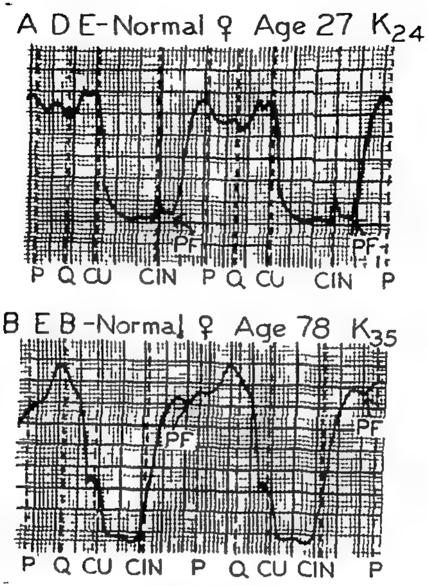

Fig 5 Paper speed of 50 mm per second The broken lines represent the onset of atrial (*P*) and ventricular (*Q*) excitation the start of the carotid upstroke (*CU*) and the carotid incisural notch (*CIN*) Arrow *PF* indicates the onset of *the up stroke which signifies the beginning of passive filling* This is the first up*stroke starting after the carotid incisural notch A From the fourth intercostal* space in the V line *B* From the fifth intercostal space in the V₃ line These traces were deliberately selected as representing an extreme example of the usual variation in the KCG with age The CIN PF interval are 0 07 and 0 18 second in the young (A) and the old (*B*) subject respectively The large outward motion starting 0 03 second before the incisura in *B* does not represent filling It is a relaxation movement and the opposite of the downstroke occurring during isometric contraction As compared to the young person (*A*) the *old subject* (*B*) also displays (1) larger atrial motions i e upstroke and down*stroke starting between* P and Q (2) much larger downstroke during isovolumic contraction (about 0 07 second after Q) this movement being only a small notch in A (3) smaller inward motion of ejection (i e the downstroke which *starts* as the carotid upstroke begins) (4) marked decrease in the size of the passive filling movement The differences illustrated although similar in type are greater in degree than those usually seen with advancing age

electromechanical lag is essentially constant at 0.038 second is almost certainly an oversimplification in view of DiPalma's evidence[14] that in cats this period may vary with changes in heart rate. The only justification for this assumption is that with our indirect methods the error involved in attempting to measure this interval for a given subject is likely to be greater than the error inherent in utilizing the average value for a large number of persons.

Our data suggest that with increasing age there is a slight trend toward prolongation of the duration of isovolumic contraction. The failure to find more striking changes in Q-CU, Q-ejection, and duration of isovolumic contraction with alterations in heart rate was surprising. The decrease in contractility with slow rates[15] would be expected to reduce the speed of the rise in pressure and thus prolong these intervals. On the other hand, the increase in filling with bradycardia tends to produce more vigorous contraction which in turn will shorten these periods. Apparently the two effects almost neutralize each other during isovolumic contraction. However, the duration of ejection is definitely prolonged at slow heart rates. These findings suggest that the mechanisms responsible for sustaining pressure may not be identical with those which are initially concerned with raising pressure.

The reports of Brandfonbrenner and associates[16] and of Foster and Reeves[17] indicated that in healthy persons stroke volume relative to oxygen consumption remains essentially constant with increasing age. Since oxygen consumption decreases, there is a slight decline in stroke volume. But the duration of ejection when considered in relation to heart rate was not reduced in older subjects. Reduced stroke volume with constant duration of ejection necessarily means a decline in the mean rate of ejection. These findings point toward a somewhat farfetched analogy with skeletal muscle and suggest that the old heart resembles the old athlete in being a poor sprinter (diminished rate of shortening or speed of ejection) but a good weight lifter (contraction well sustained).

The findings offer certain evidence concerning the controversial subject of

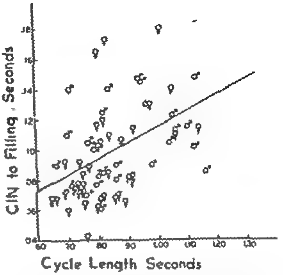

Fig. 6. Carotid incisura–passive filling interval relative to cycle length. The duration of the CIN-PF (carotid incisura to passive filling) interval is related to cycle length, but the correlation is less than that with age (Figs. 4 and 7). r = .457; y = .00975 + .10574x; σys = .0769.

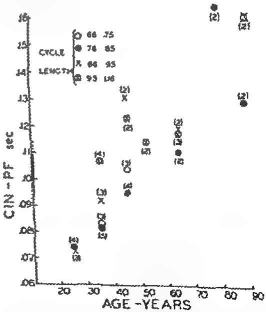

Fig. 7. Relative importance of age and cycle length in the CIN-PF interval. The points indicate average value for all subjects corresponding to that particular range of age and of cycle length. The numerals in parentheses adjacent to each symbol designate the number of values averaged to obtain that particular symbol. The data agree with those in Figs. 4 and 6 and indicate that duration of CIN-PF period is more closely related to a

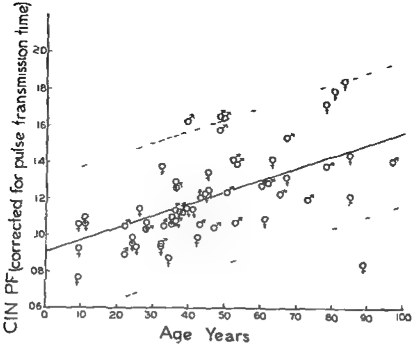

Fig 8 Duration of isovolumic relaxation in relation to age The carotid incisura to pulse filling interval (as in Fig 4) has been corrected for pulse wave velocity by adding the average pulse transmission time for age (see Fig 3 1) This correction reduces the effect of age Nevertheless the interval (isovolumic relaxation time) still exhibits lengthening with advancing years r = 58 y = 09134 + 0006x s_y = 0199

bycardia[18,19] i e the question whether the hemodynamic alterations observed in clinically *normal older persons are solely dependent on* subclinical coronary disease or also on subtle processes of unknown nature Our findings indicate that the most conspicuous feature of the normal old human heart the prolongation of isovolumic relaxation is readily demonstrable in young adults as compared to children and in premenopausal middle aged women as compared to younger women (Figs 4 and 8) Therefore the prolongation of relaxation is probably related not to coronary disease but to the aging process itself

Summary

The chief findings in healthy persons with advancing age were as follows (1) Progressive prolongation of the period of isovolumic relaxation This was relatively *independent* of heart rate (2) A steady decline in pulse transmission time (increase in pulse wave velocity) as indicated by the left ventricular recoil–carotid *upstroke in*terval Evidence is presented which indicates that the pulse transmission time is the same at the end as at the beginning *of ejection Thus the carotid upstroke–*carotid incisura interval appears to be a reliable guide to the duration of ejection (3) No significant change in the duration of ejection when corrected for heart rate (4) Slight reduction in the excitation–carotid upstroke interval However the excitation ejection time (i e the excitation–carotid upstroke interval corrected for pulse transmission time) tended to lengthen slightly with advancing age

The findings have led to the following tentative conclusions (a) The prolongation of relaxation may be a factor of some importance in regard to the relative inability of old normal hearts to tolerate tachycardia Rough calculations suggest that as an average a sustained rate of 120 or more cannot be tolerated beyond the age of 70 (b) The basic mechanisms responsible for initiating pressure for sustaining pressure and for relaxation appear to vary independently

These findings and conclusions are based

on data secured by indirect methods Pending confirmation (or refutation) by more precise techniques they should be considered as points of departure for further studies rather than as established concepts

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A computer model of atrial fibrillation

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Fibrillation can be initiated by premature excitation of some elements while others are still refractory. The induction of fibrillation should be facilitated by any agency which increases temporal dispersion of excitation and recovery.

It has been proposed that fibrillation can be initiated by unidirectional propagation of impulses about an obstacle. This mechanism can account for the rapid but still rhythmic activity of atrial flutter, but it is doubtful that a fixed circuit is compatible with the persistent chaotic activity characteristic of fibrillation.

A variant of the circus movement theory proposes that fibrillation is maintained by the irregular wandering of numerous wavelets generated by the fractionation of a wave front passing through tissue in a state of inhomogeneity with respect to excitability and conduction velocity.[1] The arrhythmia is assumed to sustain itself when the number of wavelets is so great that chance coalescence is improbable. The number of wavelets which can coexist in the tissue should be directly related to some function of the mass of the tissue and inversely related to the duration of the refractory period and to the conduction velocity.

These three functions have been demonstrated to influence the probability of persistent fibrillation in the expected manner, but direct test of the hypothesis in vivo is difficult if not impossible. We do not know, for example, the critical number of wavelets below which spontaneous recovery is likely and above which persistence is possible, nor indeed whether multiple independent wavelets exist at all. It is known, however, that (1) the atrium is not homogeneous with respect to the duration of refractory period in closely adjacent spots;[2] (2) the refractory period of the atrium is not uniformly abbreviated by vagal stimulation;[3] (3) the conduction velocity, approximately 80 cm./sec. in fully excitable atrial muscle, is depressed in the relatively refractory state; and (4) the duration of the functional refractory period is related to the preceding cycle duration.[4] Given reasonable approximations of these properties of atrial behavior, it was believed possible to construct a

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mathematical model in which the postulated mechanism of fibrillation could be tested on a digital computer.

Methods

A. The mathematical model. The model was designed on the basis of a number of simplifying assumptions. (1) The piece of atrial tissue under consideration consists of a finite number of discrete units. No fine structure is considered within a unit. (2) The units are arranged in a regular hexagonal packing as a flat sheet one unit thick. Each unit, except those on the boundary, has six neighbors (see Fig. 2). (3) A unit, when fired, transmits excitation of a constant amplitude* to all its neighbors; after some delay these neighbors will fire or not, depending on their state of excitability.

To follow the propagation process in the computer, the time as well as the tissue was considered as discrete units. The fundamental time step was chosen to give a conduction velocity of one unit per time step in fully recovered tissue. If we assume the time step to equal 5 msec., a conduction velocity of 80 cm. per second corresponds to a 4 mm. diameter of one tissue unit.

Five states of excitability were assigned as indicated in Fig. 1.

STATE 1, the absolutely refractory state, has a duration represented by the formula $R = K\sqrt{C}$, where C is the preceding cycle duration and K is a constant (K has the dimension of time). The value of K is a property of the unit and is generally different from unit to unit. A unit in State 1 will be uninfluenced by discharge of a neighboring unit.

STATE 2, the first stage of excitability recovery, lasts two time steps (10 msec.). During this period discharge of a neighbor excites the unit, but only after the lapse of 4 time steps, i.e., the conduction velocity has a lower limit equivalent to one fourth of the value obtaining in fully excitable tissue or, transposed to real tissue, 20 cm. per second.

STATE 3, second stage of relative refractoriness, is assumed to last an additional two time steps and provides for discharge after the lapse of 3 time steps.

STATE 4, persisting for two time steps after State 3, permits firing two time steps after a neighboring discharge.

STATE 5, which lasts until re-excitation, is the fully recovered state in which excitation requires only one time step per unit.

The three stages of partial refractoriness correspond to a relatively refractory period

*The assumption of constant amplitude for the action potential is a convenient simplification of relative unimportance to the operation of the model. Conduction velocity, which is the important parameter to be considered, must in real tissue be a function of the excitability of the recipient unit and of the amplitude and rate of rise of the action potential of the donor unit. It would be possible to incorporate these separate determinants of conduction velocity and [illegible] planned for a later stage of the study. Spatial and temporal summation have also been disregarded in the preliminary model.

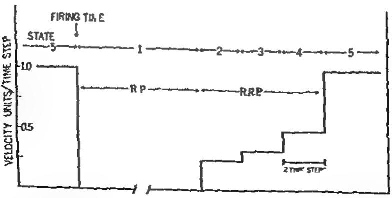

Fig. 1. Schematic representation of the five states of activity. Abscissae: time; ordinates: conduction velocity. *R P*: Duration of State 1 = absolutely refractory period. *R R P*: Duration of States 2, 3, and 4 = relatively refractory period.

of 30 msec which is close to the observed values in the exposed atria of dogs under barbiturate anesthesia and is assumed to be independent of the cycle length[5]

To start the propagation process certain units were externally stimulated It was assumed that the external stimulus was delivered at a strength so much in excess of the normal action potential amplitude that the selected tissue units unless absolutely refractory responded with a minimal delay of one time step

The only assigned variability from unit to unit was that of the parameter K The size of the tissue sheet the distribution of the parameters K and their range of variability were assumed to be primary factors in the initiation of turbulent propagation i e atrial fibrillation

B The computer program Two closely related programs were written for an I B M 650 tape system with 4 000 word drum (three tape drives) and an on line I B M 407 printer A more elaborate I B M 7090 program is now in preparation The details of these programs will be described separately[6] we outline only some of the main points here

To provide for hexagonal packing of the tissue units a 60 degree coordinate system was used In this coordinate system each unit is identified by two coordinates n and m The six neighbors of the unit (n m) then are the units with the coordinates (n m−1) (n m+1) (n−1 m) (n−1 m+1) (n+1 m) (n+1 m−1) Each of the units of the sheet was represented in the main memory of the computer by two ten decimal digit words In order to find these words in memory a mapping function was needed correlating the coordinates n m of the unit with the address in memory To permit changes of geometry a general mapping function was built into the programs The words in memory describing one tissue unit contained the coordinates of the unit its state of excitability its last time of firing the time the unit was to remain in its present state of excitability and in case a neighbor fired the time interval until the unit would fire next Other information recorded in these words was of importance only for the actual details of programming

At each time step the program searched all units in memory If a particular unit was to fire at that time step, the refractory period was calculated all excitable neighbors were stimulated and appropriate information about the firing unit was printed out Every unit not firing in that time step was checked whether subject to a change in its state of excitability As long as an external stimulus acted upon certain units of the tissue sheet these units were checked to find out whether they changed from total to partial refractoriness in which case they were stimulated to fire in the next time step Once all units had been searched the time was advanced and the process begun again

The second program permitted replication of up to 9 copies of the same tissue sheet These copies were run in parallel changes could be effected in the various copies retaining the original sheet as a control The different copies were kept on magnetic tape and were read in and processed in succession at every time step

At a later stage a visual I B M 407 printout of the tissue sheet at a given time step was incorporated (see Fig 11) This was a slow process and was used only for a few selected time steps

The I B M 650 programs were severely limited by the size of the 4 000 word main memory of the computer By using a variety of special features and in particular by applying certain overlay techniques it was possible to permit flat tissue sheets of up to 999 tissue units The first computer runs performed with these programs used a diamond shaped 31 × 32 matrix of 992 tissue units

Results

A Behavior of 992 unit matrix (Program I)

INITIATION OF SELF SUSTAINED ACTIVITY At the outset it was not known whether self sustained activity could be accommodated within the framework of 992 units The selection and distribution of the parameters K were obviously of crucial importance For the original sheet a range of values was chosen which assuming 1 time step to be equal to 5 msec would yield refractory periods in the approximate range observed in dog atria[3] The 11 values $\sqrt{10}$ $\sqrt{11}$ ... $\sqrt{20}$ were selected and

were distributed at random among the tissue units. The 11 classes of units comprised approximately equal proportions of the total population.

As in real tissue, the refractory periods (i.e., K values) assigned to the model determined the maximum frequency at which a unit could fire. For the lowest value of K the minimum cycle duration was 17 time steps (State 1 = 13 plus 4 for excitation); for the highest value the minimum cycle duration was 28 time steps. Since the maximum frequency which the whole tissue could follow uniformly was determined by those units which had the longest refractory period, the maximum regular frequency would be 1 response per 28 time steps, or the equivalent of 7.15 impulses per second. This is roughly comparable to what has been observed in the exposed dog atrium.[1]

At the start of the first run, it was assumed that the duration of the preceding cycle for all units was 40 time steps, corresponding in "real" time to a frequency of 5 per second, a frequency which the atria may be expected to follow with regularity and at uniform conduction velocity. Stimulation was applied to a cluster of 4 units at a frequency of 1 stimulus per time step. By convention, a stimulated unit having a refractory period of 20 time steps ($R = 3.16\sqrt{40}$) would be excited at time step 1, recover at time step 21, and would respond again at time-step 22. The units chosen for stimulation were selected to permit the escape of an early premature beat. Selection was necessary, for if stimulation were applied only to units with maximal K values or those surrounded by neighbors with high K values, then re-excitation could not lead to self-sustained activity; the tissue would merely be driven at the highest rate permitted by those units with the longest refractory periods. The site of stimulation was selected as a cluster containing low K values and with a pathway of neighbors of suitably low values.

Propagation of the first beat progressed uniformly at the maximum velocity of 1 unit per time step; the excitation wave reached the most remote extremity of the matrix at time step 32. The duration of State 1 ranged from 20 to 28 time steps. At the earliest possible moment, an additional response was induced in one of the stimulated units. At this moment regular and concentric propagation of the impulse was impossible because of nonuniform excitability among neighboring units. The orderly progress of the first impulse and the necessarily irregular escape of the second are illustrated in Fig. 2, which indicates those units which fired in time steps 20 to 34. The four units enclosed by the heavy beaded line were subjected to the external stimulus. Escape of the premature response occurred as individual small wave

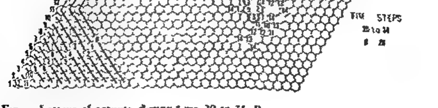

Fig. 2. Pattern of activity during time 20 to 34. Program 1. Regular pattern, labels 1-12, represent position of excitation wave of first response. Irregular patterns around stimulated unit indicate escape of premature beat.

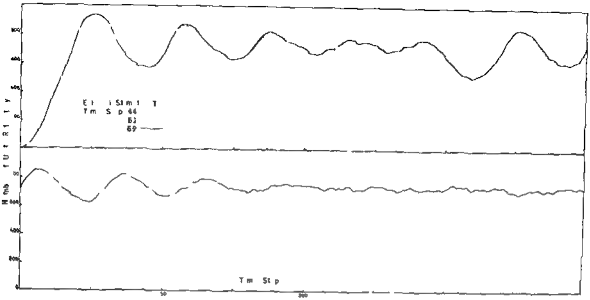

Fig. 3. Electrogram of activity in 992 unit matrix from time 0 to 400. Abortive responses are indicated by broken line.

fronts arising from the units which were fired at t=23 (3→7→11, etc.), at t=25 (... 3), and at t=30 (10→13 and 14). Because of slow conduction in the relatively refractory units near the site of stimulation, additional time was available for the recovery of more remote units; accordingly, acceleration of the premature wave fronts occurred with fusion into a single wave similar in contour to the initial one.

In preliminary trial runs the external stimulus was turned off at each successive time when any one of the four stimulated units was re-excited. Stimulation through time step 44 resulted in a single premature beat which involved the whole matrix, followed by an abortive re-entry which invaded only a few central units. Stimulation through time 61 caused two successive premature responses but again permitted re-entry of only a few units before the process expired. Stimulation through time 69 caused a self-sustained arrhythmia which persisted with no apparent tendency for spontaneous arrest for some 1,500 time steps, at which time the run was terminated.

Fig. 3 represents an electrogram of the activity through the first 400 time steps. The ordinates represent the total number of units in State 1 (i.e., depolarized) plotted against time. A flutter-like oscillation persisted until about time step 300, after which the number of active units fluctuated irregularly within a narrow range, much like the over-all electrical record of activity in fibrillating atria. The abortive responses to stimulation through times 44 and 61 are shown for comparison.

DEVELOPMENT OF ASYNCHRONY. To illustrate the influence of inhomogeneity on impulse transmission, the times of excitation and recovery were tabulated for two different groups of units for four successive discharges, including the three initial responses induced by external stimulation. A near group of 15 units fired for the first time at t=5. For comparison, a more remote group firing at t=19 was selected. The behavior of these two groups is illustrated in Fig. 4.

The proximal group is displayed in the lower half of Fig. 4 and the distal group in the upper half. In the near group the time of successive discharges was greatly influenced by the time of recovery from preceding activations, i.e., the advancing wave front was molded by the retreating edge of a prior response, so that neighboring units were forced out of phase with each other. More distant units preserved their temporal unity for a longer period, having been protected by the transmission delay near the site of initial re-excitation. The average "excitable gap" (i.e., the

interval between the end of State 1 and re-excitation) was considerably briefer for the proximal gang of units than for the distal elements. In other words, many of the distal elements were allowed time for full recovery (to State 5) before discharge of neighboring elements caused re-excitation.

Spreading of the turbulence and progressive conduction delay due to repeated premature activations is apparent in Fig. 5, which illustrates the first 5 activations of a unit on the periphery of the matrix, 21 units away from the stimulated site. The first impulse (*A*) traversed the 21 units in 21 time steps. Impulse *B* was delayed near its origin, then accelerated to full speed. To reach the same goal, *B* traversed 24 units in 31 time steps. Further delay and increasing tortuosity of the path occurred until response *E* required 75 time steps and traversed 40 units in passage.

Inhomogeneity built into the program as a range of K values was increased by re-excitation. Premature excitation resulted in a molding of subsequent responses by the recovery pattern of the preceding event (Fig. 4). As a result, dispersion of refractory periods due to variation in preceding cycle length was added to the initial *inhomogeneity*. After the lapse of 100 time steps, the average refractory period dropped to 20.4, with a range of 14-24, and the average cycle length to 27.9, with a range of 20-29. The range of variation of *cycle lengths and refractory periods then* increased progressively with time, although the mean values did not change appreciably. By time 900, some units were responding 5 times per 100 time steps, whereas others responded less than twice during the same interval. This result is in conformity with experimental observations of different frequencies recorded simultaneously from two microelectrodes inserted into fibrillating tissue.[7]

DEVELOPMENT OF CIRCUITS. It will be noted in Fig. 5 that the responses *D* and *E* were traced back to the same time of origin at $t = 69$. It is obvious that a circuit occurred in the pathway, and this can indeed be traced out. The impulse *D*, which reached the "goal" over an irregular path

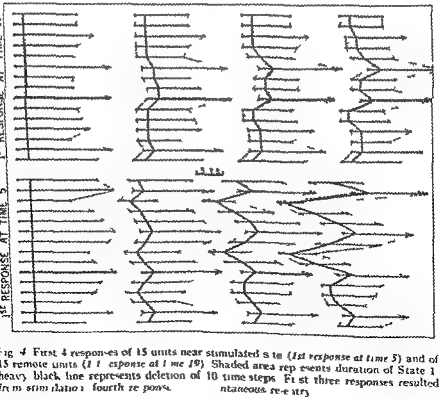

Fig. 4. First 4 responses of 15 units near stimulated site (*1st response at time 5*) and of 15 remote units (*1st response at time 19*). Shaded area represents duration of State 1; heavy black line represents deletion of 10 time steps. First three responses resulted from stimulation; fourth response ... ntaneous re-entry.

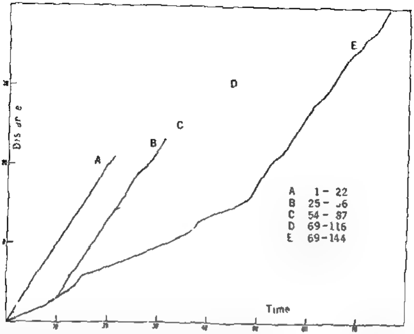

Fig. 5. First 5 responses traced to a unit on the periphery of the matrix 21 units distant from site of stimulation. Time 0 in each case represents parent response at stimulated site. Upper end of each line represents arrival at goal. Distance in units, time in steps.

iterated a vortex which again resulted in excitation of the peripheral unit. The existence of such circuits is illustrated in Fig. 6, in which the source of activity of three corner elements firing at t=857, 864, and 875 was traced through nearly 200 time steps. The routes indicated by arrows were traced backward in time, for it can be established from whence a given unit was excited, but it cannot readily be determined that a given wave front will reach a unit at some later time or indeed that the wave front will survive at all. Circuits occurred in all three pathways and all can be traced to a common origin at time 686. Each of the goal units fired several times during the period covered by the wandering of these impulses.

The fact that the excitation pathways for three widely separated units were traced back to a common trunk might suggest that a basic circuit existed which repeatedly discharged the rest of the matrix. When the self-sustained arrhythmia was initiated, and for about 300 subsequent time steps, re-excitation occurred repeatedly, although irregularly, near the stimulated site, where turbulence was most pronounced. Progressive disorganization occurred, however, and spread to all areas of the matrix with many scattered and varying sites of re-entry. Plots of the sequence of discharge of all units firing over a period of several hundred time steps failed to reveal any fixed re-entrant pathway. Many circuits developed in widely scattered areas, circuits which shifted position, frequency, and direction with time and which died and were replaced by others.

WAVE FRONTS. The nature of the simulated arrhythmia can be illustrated by plotting the wave fronts coexisting at a given instant. The term "wave front" is used to indicate those contiguous units which at a given instant are being excited by neighboring elements. Since we have decided that an element in State 2 cannot fire until 4 time steps after the discharge of a neighbor, we must include events both before and after the selected moment. Consider the wave fronts existing at the imaginary instant between time steps t and $t+1$. Any unit which fires in time step $t+1$ will be included since it must have received the impulse from a neighbor firing at t or earlier. Not all units firing in time step $t+2$ can be included, for some of these

will have received activity from neighbors firing at *t+1*, i.e., after the selected instant. Similarly, some units firing at *t+3* and *t+4* will be included in the wave front, for they will have fired in response to events at *t−1* or *t*, but others will be excluded because they responded to events at *t+1* or later.

Fig. 7 depicts the wave fronts existing between time steps 527 and 528. All units firing at 528 (labeled *8* in the diagram) are included, and those units which fired at 529, 530, and 531 in response to events prior to t 528 are also included. Contiguous units constituting an entity are enclosed by heavy beaded lines; a total of 30 wave fronts coexisted at that instant.

The further progress of any of these wavelets is indicated by small arrows. If activity passed to additional units after the moment under consideration, an arrow indicates the recipients. These waves are considered to be "active." Some wave fronts were enclosed by refractory tissue or had encountered a boundary and would therefore be snuffed out. These are considered "dead." It is apparent that fusion of some wavelets, particularly those to the

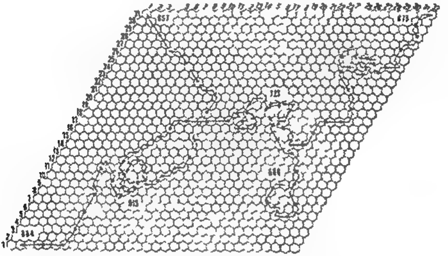

Fig. 6. Impulse pathways traced to three peripheral units firing at time 857, 864, and 875.

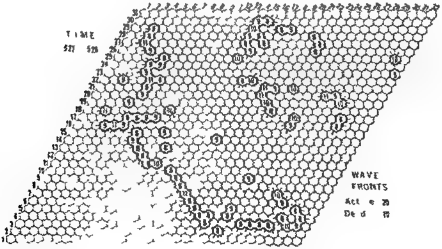

Fig. 7. Wave fronts mapped at time 528 in diagram I. Arrows indicate direction of progress of wave front; numbers indicate time (528 = 8, etc.)

left would occur within the subsequent time step, but others would become discontinuous at the same time. Similar diagrams were plotted at many times during the program. During the initial phases of the arrhythmia most of the turbulence and re-entry were confined to the region immediately surrounding the stimulated site. During this period (i.e., up to about t=300) the number of wave fronts was relatively small, ranging from 4 to 11 active, 0 to 6 "dead," and 5 to 14 total. At time step 103, for example, two large wave fronts were progressing toward the periphery in a nearly regular sweep, whereas re-entry spawned two single-unit wavelets near the site of original stimulation. A fifth wave was about to be extinguished at a boundary of the matrix.

After the development of widespread turbulence, the number of wave fronts increased, whereas the average number of units in each wavelet diminished, i.e., further fractionation occurred. Between t=300 and t=816 the number of active wavelets varied between 15 and 33 (average of 17 samples = 20.6); the number of dead wavelets varied between 4 and 16, with an average of 10.8, and the total number fluctuated between 23 and 40.

No sign of repetition of patterns was discovered, although it is certain that periodicity would eventually have to appear, since behavior of the matrix was not truly up to chance but was predestined. However, the number of permutations is so large as to preclude any obvious tendency toward periodicity.

EFFECT OF REDUCTION IN SIZE AND PROLONGATION OF REFRACTORY PERIOD. The program as developed to this point demonstrates that self-sustained activity can be induced in the matrix as designed and that in some respects the activity resembles fibrillation. The next step was to test some of the variables known from animal experimentation to influence fibrillation, namely, tissue mass, geometry, and refractory period.

A preliminary test of reduction in size and of prolongation of the refractory period was made in the first run. At t=810 the matrix was nearly bisected by removal of elements along a straight line, leaving an isthmus of 4 units in the center. The arrhythmia continued on either side of the scission. In effect, the area had been bisected for wave fronts from each side repeatedly collided with mutual extinction at the isthmus. After an additional 400 time steps the refractory periods (i.e., the K values) of all units on one side of the isthmus were increased by 50 per cent. As soon as this change in behavior became effective, that half of the matrix ceased to exhibit spontaneous activity, but it continued to be excited by impulses transmitted through the isthmus from the fibrillating portion. At t=1350 the isthmus was severed; fibrillation continued in the "control" half, but activity ceased in the altered portion, even though the latter contained the initially stimulated units and the area of earliest turbulence and re-entry.

B. Comparative behavior of smaller matrices (Program 2).

Although the preliminary results suggested that the initial matrix was larger than need be for self-sustained activity and that prolongation of the refractory period might terminate the arrhythmia, they also indicated the necessity of maintaining a control matrix for comparison with experimental patterns.

Program 2 was designed to permit a simultaneous comparative study of several matrices of originally identical geometry and parameters. One group was maintained as a control, whereas changes which might be expected to alter the arrhythmia were imposed on parallel groups. To save computer time and also to make the model more critically balanced with respect to continued activity, the matrix was reduced in mass to a regular hexagon composed of 547 units. The hexagon cut out of the original parallelogram included the area initially subjected to stimulation. The distribution of K values was the same as in the comparable area of the original program.

ALTERATION OF REFRACTORY PERIODS (PROGRAM 2-A).* As before, stimulation was continued through t=69, and a self-sustained arrhythmia resulted. By t=300, as

*Only two programs were written for these studies. In the text of the paper and in the tables and illustrations the several runs of Program 2 are identified as Program 2-A, -B, and -C.

Table I Effects of alteration of refractory periods (Program 2 A)

Group	*K (avg)*	*K (range)*	*R*	*C*	n_1	n_f	*S*	*T*	λ
2	3 46	2 84–4 07	16 8	23 6	363	23 2	54	2 34	10 1
1	3 85	3 16–4 47	19 8	26 4	384	20 7	48	2 32	11 4
3	4 23	3 48–4 92	23 6	31 2	394	17 5	40	2 28	13 7
4(A)	4 62	3 79–5 36	27 9	36 3	404	15 1	33	2 19	16 6
4(B)	4 62	3 79–5 36	28 1	36 9	365	14 8	23	1 55	23 8

K Constant in relation $R = K\sqrt{\bar{C}}$. R Average refractory period (duration of State 1). C Average cycle duration $= \frac{N}{n_f}$ where N = total number of units in matrix. n_1 Average number of units in State 1. n_f Average number of units firing per time step. S Average number of units in excited state but not yet fired. T Average excitation time $= \frac{S}{n_f}$. λ Average wave length $= \frac{N}{S} = \frac{C}{T}$.

In groups 2, 3 and 4 the values of K were changed from those of Group 1 after self-sustained activity had progressed for 300 time steps. The other values listed in the table represent the average behavior between t = 400 and t = 500 for Groups 2, 1, 3 and 4(A) and between t = 684 and 719 for Group 4(B). At the latter time, Groups 1, 2 and 3 had not changed significantly from the listed values.

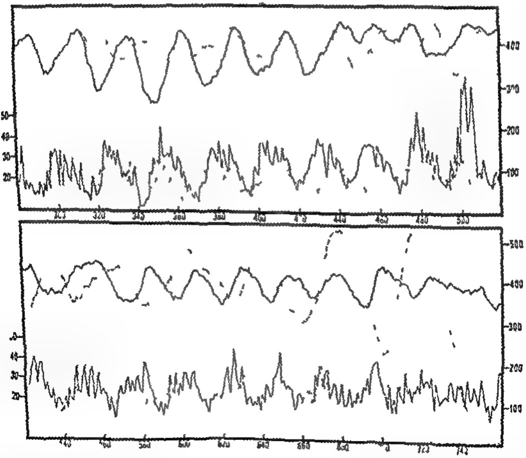

Fig 8 Electrogram of Groups 2 and 4 of Program 2 A in which K values were reduced from initial values by 10 per cent (Group 2 *solid lines*) and increased by 20 per cent (Group 4 *broken lines*). Change in K values instituted at time 300. Upper curves number of units in State 1 (scale at right); lower curves number of units firing in each time-step (scale at left).

in the first program, turbulence was widespread and a diagnosis of fibrillation was made. At that time the program was replicated to create 4 groups, all of which started in the same condition. Group 1 was continued with the original K values; in Group 2, all K values were reduced by 10 per cent; in Groups 3 and 4, the K values were increased by 10 and 20 per cent, respectively. At t=730, Group 4 ceased firing.

It should be pointed out that inhomogeneity, the *sine qua non* of inducing sustained activity in the model, was retained in all groups; the refractory periods of all units were altered in proportion. It follows that for a given area and configuration of the model, the likelihood of continued self-sustained activity was reduced by prolongation of the absolutely refractory period.

Fig. 8 illustrates the behavior of Groups 2 and 4 (the extremes of the K values) after the parameters were changed. Oscillation of the number of units active in Group 4 became accentuated beginning at about t=580 as the active wave fronts began to coalesce.

A statistical comparison of the effects of alteration of the refractory periods is presented in Table I. The average and range of K values for the various groups are the independent parameters introduced at time 300. The computed parameters R, C, n_1, n_f, S, T, and λ are listed for Groups 2, 1, 3, and 4(A) as average values derived from 5 samples of 16 consecutive time steps each, taken between t=400 and 500. The values tabulated for Group 4(B) are the average for these same parameters over 36 consecutive time steps (684 to 719) shortly before spontaneous arrest. Between t 400 and 500 the four groups had become differentiated with respect to the computed parameters, but Group 4 had not yet clearly exhibited the signs of progressive organization which preceded its arrest.

It is predictable that increasing the value of K must increase the average refractory period (R) and cycle duration (C). The average frequency of excitation, in other words, must diminish. Accordingly, given a fixed number of units, the increased refractory periods must be accompanied by a reduction in the average number of units firing per time step (n_f). The value of n_f was roughly inversely proportional to the average K value in the four groups. One might also expect the average number of units in State 1 (n_1) to be increased by prolongation of the refractory period, but since fewer units entered State 1 during each time step as the average value of K was increased, the difference between the several groups was not great, ranging from 363 in Group 2 to 404 in Group 4.

It was expected that the progressive organization of activity preceding arrest in Group 4 (highest K value) would be accompanied by a progressive increase in the conduction velocity, i.e., by a decrease in excitation time. At time 400 to 500, however, this trend was not yet apparent. The average excitation time, T, is represented by

$$\frac{(4n_2 + 3n_3 + 2n_4 + n_5)}{n_f}$$

where n_2, n_3, n_4, and n_5 represent the number of units firing per time step from States 2, 3, 4, and 5, respectively, and n_f represents the total number of units firing per time step. The sum ($4n_2$ + $3n_3$ + $2n_4$ + n_5) is represented in the table as S. There is no significant systematic relationship between the average K and the average excitation time in the several groups. Shortly before arrest of Group 4, however, mean conduction velocity did indeed increase (Group 4(B), t=684 to 719).

The values for wave length (λ) in the table are average values computed from the ratio of N (the total number of units in the matrix) to S (the number of units in the excited state, i.e., the number of units comprising wave fronts).* The average value of λ increased in proportion to the value of K.

Details of the events prior to arrest of Group 4 are displayed in Fig. 9, which

*Since it may not be immediately apparent that the ratio N/S yields λ, the following derivation is appended. Let S = the average number of stimulated units, T = the average excitation time, and n_f = the average number of units firing per time-step. Then, $S = n_f T$. The average cycle duration, C, can be defined as $\frac{N}{n_f}$ where N represents the total area of the matrix. The wave length, which is equal to velocity divided by frequency, must also be equal to cycle duration (reciprocal of frequency) divided by excitation time (inverse of velocity). Accordingly, $\lambda = \frac{C}{T} = \frac{N}{n_f T} = \frac{N}{S}$.

encompasses the last major excitation process in that group At the start of the figure the number of units firing was at a low ebb falling to one or two units per time step This was at a time when a single re entrant circuit was progressing not far from one corner of the matrix During the time that this excitation process was slowly escaping through a barrier of relatively refractory units (excitation time averaging more than 2 5 time steps per unit) more peripheral units were emerging from the refractory state The fractionated wave fronts progressed more and more rapidly merged and eventually swept out the whole matrix at full speed The number of units firing increased to more than 30 per time step average excitation time decreased to 1 3 time steps per unit and the number of units in State 1 increased rapidly As the united wave front encountered the boundary of the matrix the number of firing units rapidly declined until the excitation process died out

Over the span of 36 time steps represented in Fig 9 the average number of units in State 1 was 365 significantly less than at the time of the sample 4(A) in Table 1 The average figure is relatively less significant than the fluctuation of that number but even the apparently periodic behavior in Fig 8 is not necessarily indicative of periodically repetitive activity Periodic behavior in the model could be accompanied by little or no fluctuation of the electrical correlates of activity whereas aperiodic behavior could result in wide oscillations For example it is true that a stable circus movement flutter about an obstacle eccentrically located in a relatively small matrix would yield waves of regular amplitude contour and period but it is also true that the swings would be damped out if the obstacle were centrally located or if the matrix were great in area It could be shown that the increasing amplitude of oscillations of Group 4 was associated with a progressive decrease in the number of vortices until at the time represented in Fig 9 a single re entrant circuit accounted for the last major activation of the model It is apparent then that the shrinkage of turbulence imposed by the increased K value left a large area of the matrix free to recover to State 5 and to respond at full velocity Re entrant activity was wiped out as inhomogeneity of excitability was erased

The very slight effect of K on conduction velocity while turbulence was still manifest in all groups merits some detailed analysis Short of arrest of turbulent activity it can be shown in a reduced model that alteration of the refractory period should not

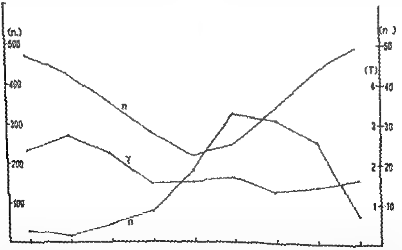

Fig 9 Group 4 Program 2 A events from t = 684 to 719 just prior to spontaneous arrest Abscissa time intervals of 4 time steps Ordinate number of units in State 5 (n_r) number of units firing per time step (n_f) average excitation time (T) Each plotted value represents the average of 4 successive time steps

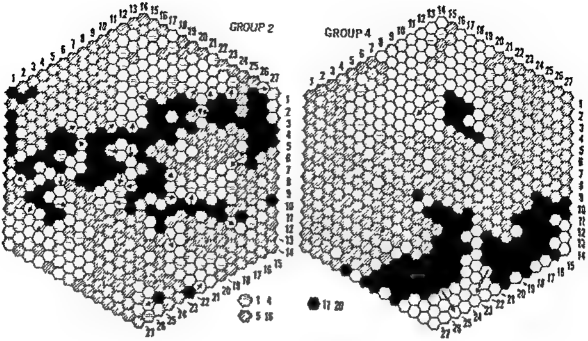

Fig. 10. Comparison of Group 2 and 4 of Program 2-A shortly before arrest of activity in Group 4. Group 2 on left, time 578-597 inclusive (578 = 1). Group 4 on right, time 656-675 (656 = 1). Arrows indicate direction of further activity.

significantly alter the average excitation time. In a cluster of units having the same refractory period determined by K = 5, consider 12 arranged in two contiguous columns of 6 units each, such that unit 1 is a neighbor of units 2, 3, and 4. Assume that one-way transit has been established up one column and down the other, with a conduction time of 3 time steps per unit. Total circuit time will be 36 time steps and the refractory period will be $5\sqrt{36}$ or 30 time steps. If, now, the value of K were reduced by 10 per cent, to 4.5, a "short circuit" would occur, resulting in a 10-unit path. Total circuit time would drop to 31 time steps and the refractory period to 25 time steps, but the average conduction time would increase to only 3.1 time steps per unit. Conversely, an increase of K by 10 per cent would result in an addition of one unit to the path length. Total circuit time would increase to 41 time steps, refractory period to 35 time steps, and the average conduction time would become 3.15 time steps per unit. If the system were more finely resolved, it is apparent that the net effect of a change in K would be a corresponding change in refractory period, transit time, and path length *without any change in excitation time*. The data of Table I show that the average behavior of the four groups of Program 2 at t 400 to 500 fits this reduced conjectural model. The average wave length increased with the value K, and a further increase occurred in Group 4 as turbulence diminished, conduction velocity increased, and wave fronts coalesced.

Coalescence of wave fronts is illustrated by Fig. 10, which compares Groups 2 and 4 at a time shortly before the spontaneous arrest of the arrhythmia in Group 4. The times were not identical, for Group 4, with higher K values, was forced to operate at a slower average frequency than Group 2. Accordingly, a time was chosen when a particular "indicator" unit had fired in both groups for the twenty-second time. In each matrix the units which fired during a span of 20 time steps are represented as crosshatched areas (time t+1 to 4), diagonally striped areas (time t+5 to 16), and black areas (t+17 to 20). Where the black areas, *which include the advancing* wave fronts, are separated from the Class 1-4 by white areas, potential sites of re-entry exist. In Group 2, in which the average *refractory period* was less than 17 time

steps re-entry was possible without an intervening white area in Group 4 with an average refractory period of 28 time steps, re-entry could not occur without at least one intervening white unit In Group 4 waves of activity swept downward on both sides converged in the center and emerged at the top of the diagram as a single wave front which accomplished one more activation of the matrix before expiring

EFFECT OF UNIFORM K VALUES (PROGRAM 2 B) An additional series also starting with 4 groups under initially identical conditions was set up to test whether abolition of the inhomogeneity of K values would alter the behavior of the tissue Group 1 was maintained as a control At t=300 all K values in Group 2 were changed to the average of K values in the control group namely 3 85 In Groups 3 and 4 they were reduced to 3 5 and 3 16

At the outset all groups were inhomogeneous because of a range of K values to which was added the dephasing due to variation in the preceding cycle lengths for individual units It was expected that the assignment of constant K values would reduce the inhomogeneity that is the cycle lengths would become equal After the lapse of about 300 additional time steps the variation in cycle lengths disappeared in Groups 2 3 and 4 Periodicity however also became apparent Exact repetition of behavior was not apparent during the time the program was allowed to run, but in Group 3 an approximate period of 84 time steps (involving on the average 4 successive excitations) was discerned Repetitive circuits occurred at several sites in the matrix Because the parameters of all units were equal exact periodicity at some multiple of 21 time steps should be expected The run was terminated when it was decided that spontaneous arrest was unlikely

In Fig 11 the behavior of the control group in which the average value of K was 3 85 is compared with Group 2 in which all units were assigned the value K = 3 85 The two patterns are reproductions of the I B M 407 printout sheets taken at time step 1505 Units labeled *S* represent those units which have been stimulated but have not yet fired Contiguous *S* units are outlined to indicate the number of wave fronts coexisting at the selected moment

In this program a given unit would be expected to fire repeatedly with the same cycle length many electrodes spotted at various points on the surface would yield the same frequency In other words the deliberate introduction of *homogeneity* resulted in periodicity more characteristic of flutter than fibrillation

EFFECT OF CHANGES IN GEOMETRY (PROGRAM 2 C) In the final run of this series an attempt was made to study the influence of the size of the matrix Group 1 of the

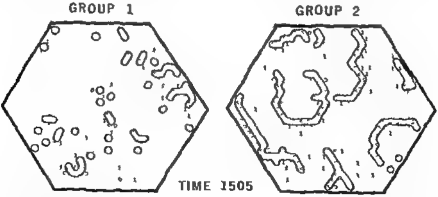

Fig *11* Sample of hexagonal printout for Groups 1 and 2 of Program 2 B *Group 1* control with unchanged parameters Group 2 all K values changed to 3 85 (mean of values in Group 1) Printed characters indicate state of activity *0* = excitable (i e units in States 2 3 4 or 5) *1* – refractory (State 1) *S* = units excited but not yet fired *F* = units firing in that time-step (time 1505) *S* units are outlined to define coexisting wave *fronts*

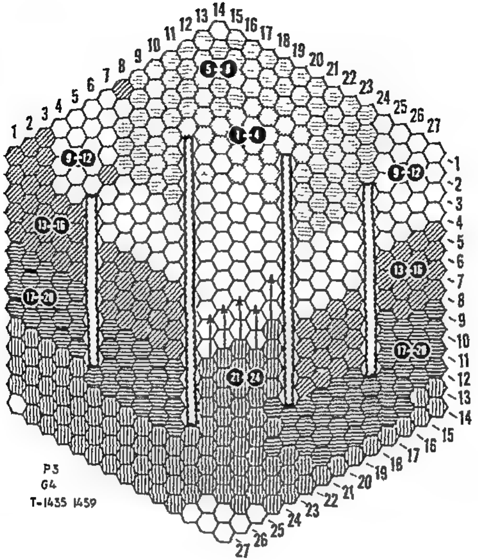

Fig 1 Circus movement flutter in Group 5 of Program 2 C Arrows indicate direction of advancing wave front

strates that something akin to fibrillation can sustain itself in a limited system in which inhomogeneity comparable to that observed in exposed dog atria is built in

Differences between the model and real tissue In many respects the model departs from the structural and functional characteristics of living tissue One of these although perhaps not of cardinal importance in an assessment of the validity of the hypothesis is the geometry The model is a flat sheet Topologically it could be assumed to be a sphere with a large obstacle but the perimeter of the obstacle unlike the boundaries of the several orifices in real atria is large with respect to the total mass of the sheet Closer simulation could be incorporated in a more complete program for example all units on one margin of the original sheet could be made neighbors of the units of the opposite edge all margins could be fused to create a sphere with or without orifices the sheet could be folded to simulate a three-dimensional system two or more units thick Until these extensions of the program have been studied it is difficult to predict their influence on the activity of the network For example in the present simple sheet it has been obvious that many marginal

units did not participate fully in the turbulent activity characteristic of the interior of the model. Presumably this is because, having fewer neighbors, they were exposed to fewer possible routes for re-entry.

The packing of units in the model was arbitrarily chosen to provide six neighbors for each internal unit. We do not know how far this may depart from the functional anatomy of atrial tissue, but systems with smaller or greater numbers of potential contacts can be readily devised.

The model differs from living tissue in physiologic as well as anatomic features. Inhomogeneity was introduced as a random distribution of K values. Once assigned, these values remained attached to the individual unit, except for major changes introduced for specific study. It is certain, however, that the K values in real tissue cannot be invariant. Irregular fluctuations of local refractory periods might be expected to favor persistence of truly turbulent activity.

No preferential conduction pathways were incorporated into the model, although evidence indicates that the propagation of impulses in living atria is not uniform in all directions from a stimulated site. Conduction velocity is faster in the direction of the longitudinal axes of the trabeculae than transversely.[8] This feature would probably be of little significance in the model if we assume, for example, that the tissue units are longer in the *n* axis than in the *m* axis of the matrix; then the velocity of propagation is faster in that direction.

The model was constructed with fixed definition of neighbors and with no provision for temporal or spatial summation. Models of nerve nets incorporating summation together with axonal transmission from remote units have been constructed and have been shown to exhibit more or less rhythmic self-sustained activity.[9] It is perhaps significant that the atrial model is capable of fibrillation without the incorporation of these additional complexities.

Analysis of turbulent impulse propagation. Admittedly, the model bears only a superficial resemblance to real atrial tissue. Nevertheless, it provides a means of examining some features of propagation in a nonuniform two-dimensional excitable medium in a manner which cannot be approached in living tissue.

The model illustrates that re-entrant circuits can be generated without an anatomic obstacle. Islands of refractory tissue have long been assumed to provide opportunities for circuit formation, although it is commonly supposed that such islands result from pathologic alteration of the properties of the tissue, and that the resultant circuits continue as fixed sources of repeated excitation of the atria or, in effect, pacemakers. In the model, numerous vortices shifting in position and direction like eddies in a turbulent pool accounted for the sustained activity in all programs except those in which the parameters were changed to permit fixed circuits.

Inhomogeneity was clearly necessary for the induction of self-sustained activity in the model and must be responsible for continued turbulence, but inhomogeneity was not necessary for perpetuation of a periodic flutter-like process. In the groups in which all K values were made identical, two or three residual circuits continued to operate through fixed pathways of 5 or 6 units. These conditions were grossly artificial, for exact uniformity could hardly be expected in a biologic system. If the values of K, instead of being made identical, were limited to a narrower range about the same mean value (3.85) as the control group, it is possible that the model would show an increase in apparent periodicity and a decline in turbulence. In other words, there might be no sharply defined boundary between what we may call "true" fibrillation and "true" flutter. At least in this respect the model appears to resemble certain cases of atrial dysrhythmia as observed in the clinic.

The statistical comparison in Tables I and II permit conjecture of the nature of turbulent activity in the model and of the influence of the induced alterations in K values and size upon it. It is clear that if turbulence is characterized by drifting eddies or wave fronts, then some spatial latitude is necessary for persistent activity. To cite the extreme case, turbulence cannot be maintained in a single column of cells, even if the ends of the column were joined to form a ring; only periodic activity

would be possible. In other words, not only the total area (N) but the *shape* of the matrix is important. In the regular hexagon of unit thickness used in the present studies the latitude or space available for turbulent activity must be some function of the radius or total area but it is apparent that the space factor would be a different function of area in matrices of different shapes. Two hexagons of equal area connected by a narrow isthmus would not be expected to sustain turbulent activity any more readily than either member alone. The probability of self sustained aperiodic activity should be related therefore to the area or mass of the matrix multiplied by a constant which would be characteristic for a given shape. The preliminary correction for shape (N P) as listed in Table II cannot be universally applicable for such a ratio would be infinity in a closed spherical surface yet a small sphere would be unlikely to support self sustained turbulence.

Persistence of arrhythmia was clearly related to the mean value and the range of the assigned K values, i.e., upon the duration of the refractory periods. Fibrillation could not have been induced without the initially programmed inhomogeneity and the self sustained activity quickly became organized and periodic when the K values were equalized. It is safe to conclude that persistence is directly related to some function of the range of K and inversely related to some function of the mean value. The precise definition of the appropriate functions, however, is not yet apparent. For example, persistence is not simply related to the ratio of the range of K to the mean of K, for this ratio was constant in the four groups of Program 2 A (Table I). Nor does the range of K describe the full influence of the frequency distribution and the random geometric distribution of the 11 families of K. If, for example, only the classes $K = \sqrt{10}$ and $K = \sqrt{20}$ were included and if all the values $\sqrt{10}$ were placed on one side and all the values $\sqrt{20}$ on the other side of a dividing line, then turbulent activity would surely be impossible, yet the range and the mean of K would be the same as in Program 1. Some function of the range would therefore have to take into account the range, frequency distribution and random disposition of K values.

It is probable that the influence of the range of K becomes incorporated into the dependent variable T. It was shown in Table I that the average value of T did not change very much as the value of K increased and an argument was presented to explain the apparent insensitivity of that parameter. It should be obvious that during self sustained activity a wave front will move at the maximum velocity permitted by the state of recovery of the surrounding units and that re-entry of any given unit in a circuit will correspondingly occur over the briefest (not necessarily the *shortest*) possible pathway. If such a path way includes units with different values of K, as it must do in the several groups of Program 2 A, then the conduction velocity cannot be constant. The impulse will be maximally delayed by units which are in State 2 and will accelerate when traversing units in a more advanced stage of recovery. The mean excitation time will accordingly have to be less than 4 and more than 1 but the range of T will be wide. If all the values of K are made equal, as in Program 2 B, the briefest path will also be the shortest in distance but the excitation time at each unit in the circuit will be maximal. On the other hand, in the group in which a stable circus movement resulted the excitation time was reduced to the minimal value of 1 in all but a few units. In the latter case the programmed inhomogeneity, although still present, was no longer operative; nearly all units were in State 5 when the excitatory process reached them. In both cases self-sustained activity continued but in a completely periodic manner. Turbulence, in other words, was eliminated when inhomogeneity with respect to conduction velocity was abolished whether by eliminating the initial variation of K values or by introducing anatomic barriers.

The inhomogeneity with respect to conduction time can be expressed as the standard deviation of T. This deviation is the result of the programmed spread of K values but it is also influenced by the geometric configuration. A wide range of K has no significance if the system is driven at slow frequency, for all units will re-

on the particular point and on the time. Two geometrically similar continuous models will exhibit a dynamically similar propagation pattern if at all corresponding points the above dimensionless numbers are identical for all corresponding times.

For the discrete model this does not immediately apply, since point by point dynamic similarity cannot exist unless the models are geometrically equal (not just similar). However, in similarity with the properties of the Reynolds number one may conjecture that the number indicates whether the propagation pattern in a continuous model is laminar or turbulent. For the discrete model we may ask whether instead of a local fibrillation number changing from point to point a suitable global index exists which indicates whether propagation is laminar or turbulent. As such a global index one might use the average of the individual local fibrillation numbers. However, the discussions presented earlier suggest that an empirical relationship which permits comparison of some of the groups of Program 2 may be expressed in the form

$$F = \frac{L\sigma_T}{\overline{K}^2}$$

where σ_T represents the standard deviation of T and $\overline{K}$ represents the average value of K. This dimensionless index is obviously related to the local fibrillation number LT/K^2 but further study of the model and its mathematical properties will be necessary to arrive at a clearer understanding of these numbers and their properties as indicators of laminar or turbulent propagation patterns.

Application of this formula to the results obtained in the groups studied so far is illustrated in Table III. The expression A/P (i.e. the ratio of area to perimeter) is substituted as a convenient approximation of L, recognizing that it cannot be strictly appropriate for comparison of dissimilar groups. The data suggest that the critical value of F is close to 0.5 within the four groups of Program 2A in which only the assigned values of K were changed and in Groups 1, 2 and 3 of Program 2C which differed in size but not in shape. Groups 4 and 5 of Program 2C, in which internal obstacles were created, cannot be directly compared with each other or with the other groups but in Group 4 arrest or periodicity was approaching and in Group 5 a circus movement flutter had established itself at the time of the samples from which the tabulated values were calculated. Group 2 of Program 2B had also become periodic.

The wavelet hypothesis. Beyond providing an opportunity to relate the number of individual wave fronts to various induced alterations in the parameters of the matrices, the model adds little to the wavelet

*Table III. Average values used in calculation of F'**

Group	A/P	T	σ	$\overline{K}^2$	F	Remarks
2A 2	7 0	2 34	1 20	12 0	70	
2A 1	7 0	2 32	1 23	14 8	58	
2A 3	7 0	2 28	1 25	17 9	49	
2A-4(A)	7 0	2 19	1 23	21 3	40	
2A-4(B)	7 0	1 55	1 04	21 3	34	Arrested
2C 1	7 0	2 32	1 23	14 8	58	
2C 2	6 5	2 02	1 18	14 8	52	
2C 3	6 0	1 95	1 13	14 8	46	
2C 4	4 7	1 89	1 13	14 8	32	
2C 5	2 [illegible]	1 08	28	14 8	05	Periodic
2B 2	7 0	3 96	21	14 8	10	Periodic

1 relat... $F' = \frac{L\sigma_T}{\overline{K}}$ Samples ... same time pa... rr pe d ... groups in Table I and II A/P has been used as approx... m ti... of L

hypothesis as originally proposed. Alterations expected to reduce the likelihood of persistence (increased refractory period, decreased size) do indeed reduce the number of wavelets, but it is apparent that a mere numerical tally provides neither an adequate description of mechanism nor a basis for predicting future status. Numerous wavelets, fractionated in the sense of noncontiguity, may represent fragments of a relatively uniform process sweeping across relatively large areas without providing opportunities for re-entry. In other words, a single impulse generator beating at a sufficiently high frequency could yield as many individual wavelets as the more complex self-sustained activity described above. Previously published studies have indicated the superficial similarity but difference in mechanisms between these two forms of dysrhythmia. To assess the functional significance of the number of wavelets in existence at a given moment it would be necessary to know their past history and future course, attributes difficult to describe quantitatively. In short, the model supplies insight into possible mechanisms of sustained turbulent impulse propagation, but has not yet provided a stringent and exclusive definition of fibrillation.

Summary

A mathematical model of impulse propagation in a nonuniform two-dimensional system was prepared as a program for a digital computer. The model exhibited self-sustained turbulent activity having many similarities to atrial fibrillation. The activity was not the result of fixed impulse generators or circuits, but was sustained by irregular drifting eddies which varied in position, number, and size. Increasing the refractory periods while retaining nonuniformity resulted in arrest of activity. Restoration of absolute uniformity resulted in periodic activity characterized by fixed re-entrant circuits without obstacles. Reduction of the area of the model altered the self-sustained activity in the direction of arrest, and the creation of internal obstacles resulted in a periodic circus movement flutter. The behavior of the model suggests the formulation of a "fibrillation number" similar in concept to the Reynolds number related to turbulence in fluid flow.

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The effects of prolonged hypomagnesemia on the cardiovascular system in young dogs

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Although magnesium is second only to potassium in abundance in intracellular fluid, it was not until 1932 that Kruse, Orent, and McCollum[1] established it as a cation essential to life. Since then the biologic functions of magnesium, especially as an activator in biochemical systems, has been a subject of intensive investigation. The rapidly growing literature on the metabolism of magnesium and its relation to other dietary constituents has been reviewed recently by Wacker and Vallee[2,3] and O'Dell.[4] The biologic effects of a dietary deficiency of magnesium had been studied in a variety of animals, especially in rats,[5-8] and only to a limited extent in dogs.[9,10] In the species studied, a variety of pathologic lesions have been reported, especially calcification in the heart and kidneys. Little information was available concerning the gross and microscopic alterations due to magnesium deficiency in dogs.

This present investigation was undertaken to study the effect of magnesium deficiency in the production of histologic lesions in the cardiovascular system of the dog and to attempt to correlate these findings with the electrocardiogram and with the level of certain plasma constituents which have a relationship to normal and abnormal cardiac function.

Since this study was started, Vitale and associates[11] have reported their findings on magnesium deficiency in puppies. They demonstrated calcification of the aorta and medium-sized arteries, including the coronary arteries. They also noted calcification in the inner portion of the myocardium. More recently a study of magnesium deficiency in weanling puppies by Bunce and associates[12] demonstrated calcification of the aorta with no gross or microscopic lesions in the heart.

Methods and materials

Thirty mongrel dogs approximately 3 to 8 months old and weighing 10 to 16 pounds were divided into control and test groups. All animals were kept on the same magnesium-deficient diet and fed ad libitum. In the control groups (10 animals)

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Table I. Composition of diet containing all necessary minerals, vitamins, and other nutrients with the exception of magnesium salts

Low magnesium diet—Composition of 1 pound of diet	
Casein (purified)	0.20 lb
Corn oil	0.20
Dextrose	0.485
Gelatin	0.05
D L Methionine	1.36 Gm
Salt mixture	
Calcium carbonate	9.06 Gm
Monocalcium phosphate	2.27 Gm
Copper sulfate	9.20 mg
Manganous sulfate	0.12 Gm
Ferric citrate	0.845 Gm
Potassium iodide	0.025 Gm
Potassium phosphate	2.27 Gm
Sodium chloride	5.07 Gm
Zinc carbonate	7.60 mg
Vitamins	
Vitamin A concentrate (200,000 U/Gm.)	0.045 Gm
Vitamin D concentrate (400,000 U/Gm.)	0.0075 Gm
Alpha tocopherol	0.05 Gm
Ascorbic acid	0.45 Gm
Inositol	0.05 Gm
Choline chloride	0.75 Gm
Menadione	0.0225 Gm
Para aminobensoic acid	0.05 Gm
Niacin	0.045 Gm
Riboflavin	0.01 Gm
Pyridoxine hydrochloride	0.01 Gm
Thiamine hydrochloride	0.01 Gm
Calcium pantothenate	0.03 Gm
Biotin	0.20 mg
Folic acid	0.90 mg
Vitamin B_{12}	0.0135 mg

a magnesium supplement was added to the drinking water daily as 100 c.c. of 10 per cent magnesium chloride. There was no forced feeding of the drinking water and the animals did not drink all the water given to them every day.

The magnesium-deficient diet had the composition noted in Table I and was essentially a balanced diet which contained all the necessary minerals, vitamins, and other nutrients with the exception of magnesium salts. Essentially, it consisted of protein (20 per cent) in the form of purified casein, fat (20 per cent) in the form of corn oil, and carbohydrate (48.5 per cent) in the form of dextrose. Gelatin and salt mixtures and vitamins were added in proportion as outlined in Table I. Changes in weight and objective manifestations of magnesium deficiency were recorded throughout the experiment. Various analyses of blood to determine the levels of serum sodium, potassium, chloride, cholesterol, calcium, and inorganic phosphorous were made approximately every 2 to 4 weeks and again whenever possible from 1 to 4 days prior to spontaneous death of the animal. In the other animals blood was taken just prior to the time of sacrifice. Serum sodium and potassium was determined by flame photometry. Serum chloride was determined by mercurimetric titration. Serum calcium and magnesium were estimated by the Clark-Collip[6] and titan yellow procedures[7,8] respectively, and inorganic phosphorous by the Fiske and Subbarow[9] procedure. Serum cholesterol was determined by the method of Abell.[10] Serial electrocardiograms were recorded every 2 to 4 weeks in 15 of the animals, 5 of which belong to the control group.

Of the control animals, 2 died of pneumonia after 50 days. Two control animals were subsequently placed on a magnesium-deficient diet after they had thrived well for 13 months, and the other control animals were sacrificed at irregular intervals. The oldest dogs were allowed to live for 780 and 791 days, respectively. The average survival of the control dogs was 318.1 days. In general, the test animals were allowed to live until they died of magnesium deficiency. In this group of 20 animals, 2 died of pneumonia. The test animals lived from 40 to 158 days, with an average of 87.2 days. It should be noted here that in 8 of the magnesium-deficient animals which were approximately 3 to 4 months old, the average survival was only 60 days.

Results

General effects. Throughout the experiment it was noted that the animals which were fed a magnesium-deficient diet showed a pattern of retarded growth when compared to those which were fed the same diet plus magnesium in their drinking water. Magnesium-deficient animals con

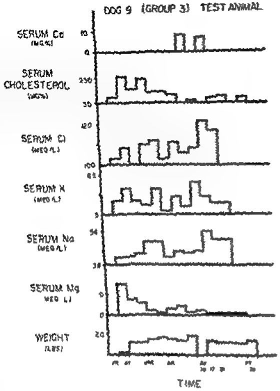

Fig 1 In this test animal the level of serum magnesium dropped to below 0 5 Meq /L and remained there The hypomagnesemic state resulted in a poor growth pattern There was no definite influence upon the serum potassium sodium or chlorides The levels of serum cholesterol showed an initial increase but this was not sustained (The black dots in the chart indicate the levels of serum electrolytes taken for a base line 3 weeks before the experiment was started)

tinued to grow regularly for the first 2 to 4 weeks then their weight level reached a plateau and remained there for several weeks and gradually declined for the remainder of the experiment (Fig 1) In contrast the animals which were fed a magnesium-deficient diet plus magnesium in their drinking water showed a steady increase in weight and achieved a normal size for this type of dog (Fig 2)

Loss of hair was characteristic in the magnesium deficient group of animals The loss of hair occurred generally over the whole body but was especially marked over the abdomen and the front and hind legs (Fig 3) It was also noted about the ears tail and occasionally the eyes The loss was frequently very extensive and large areas became completely denud

The skin in the denuded areas seemed to be somewhat greasy in appearance and frequently progressed to ulceration Another characteristic of the magnesium deficient dogs was the altered appearance of the extremities The paws were swollen especially the forepaws with marked spreading of the phalanges Instead of walking on their paws the animals appeared to be walking on their wrists That is they appeared to be bearing most of their weight on the metatarsals These changes were most pronounced in the forepaws and were associated with a horizontal curvature of the nails In many animals especially in the advanced stage of magnesium deficiency there was an associated weakness in the hind limbs so much so that at times they had great difficulty in supporting themselves (Fig 3)

In some of the magnesium deficient animals some evidence of hyperirritability

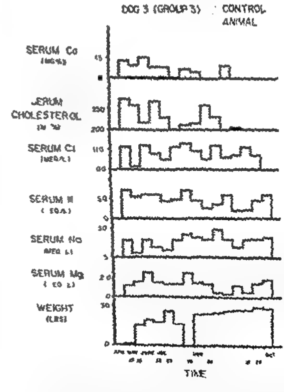

Fig 2 Control animal which was given added magnesium in the drinking water Note the steady gain in weight associated with normal level of serum magnesium There is a marked variability in the levels of serum cholesterol (The black dots in the chart indicate the normal electrolyte values 2 weeks before the onset of the experiment)

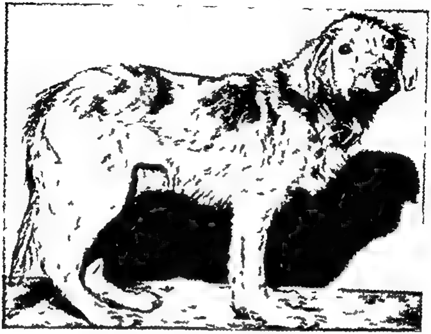

Fig. 3 Hypomagnesemic dog. Note the widespread loss of hair, poor nutrition, edema of the forepaw with marked spreading of the phalanges and curvature of the nail. Note also the weakness of the hind leg.

could be noted. Exaggerated and at times generalized spastic responses were obtained to ordinary noxious stimuli. These signs were not sought for in all animals. Many of the magnesium-deficient dogs developed convulsions at least once during the course of the experiment. Four of the magnesium-deficient animals died soon after their first convulsion. The others survived the first convulsion by many days or weeks. It is not possible to say whether convulsions were present in all animals prior to death, since several of these dogs died during the night or on the weekend when it was not possible to observe them.

In the magnesium-deficient animals which were approximately 4 to 8 months old at the onset of the experiment the survival time ranged between 40 and 158 days, with an average of 87.2 days. In 8 of the deficient animals which were under 4 months of age at the onset of the experiment the average survival was only 60.2 days. In 2 older dogs which were 16 and 18 months old at the onset of the experiment, survival on a magnesium-deficient diet was 10 and 11 months, respectively.

In the control group all animals showed a normal pattern of growth and weight and seemed to thrive very well on a magnesium-deficient diet with the addition of magnesium to the drinking water. These animals were not hyperirritable and did not have any convulsions. The total number of days in experiment ranged from 48 to 791 days, with an average of 318.1 days. These animals were allowed to survive for approximately four times the duration of magnesium-deficient animals without any signs or symptoms of magnesium deficiency.

Electrolytes. The normal values for serum magnesium by the method used in this experiment was 1.6 to 2.2 mEq. per liter. In the magnesium-deficient dogs the level of serum magnesium dropped to a very low value, below 0.5 mEq./L., within 3 to 6 weeks after the animals had been placed on a special diet, and it remained there for the duration of the experiment. In the control group the serum magnesium remained within normal limits throughout the experiment, except for several instances in which there was a transitory drop to about 1.0 mEq./L. due to an inadequate intake of water. These levels returned to normal as soon as the amount of magnesium was increased in the drinking water. There was no apparent effect of magnesium deficiency on the levels of serum potassium, chloride, or sodium

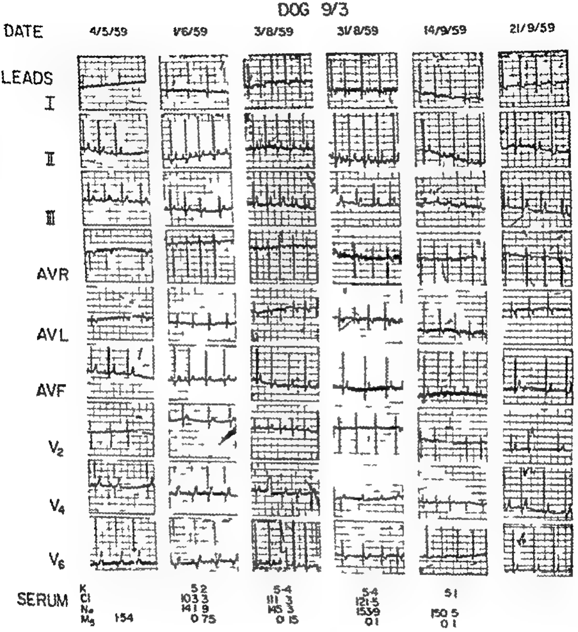

Fig. 4 Serial electrocardiogram showing no direct correlation with the level of serum magnesium. Note in the V lead that the T waves revert to normal in the presence of a persistent hypomagnesemia.

concentration In the magnesium-deficient group of animals the levels of serum calcium appeared to be slightly lower than those found in the control group Serum calcium for the deficient group of animals was 9 37 mg per cent with a standard deviation of ±1 08 In the control group the serum calcium was 10 4 mg per cent with a standard deviation of ±0 96. The of inorganic phosphorus in the deficient group was 6 07 with a standard deviation of ±1 33 whereas in the control group of animals the level was 5 83 mg per cent with a standard deviation of ±1 37 There was a marked variability in the levels of serum cholesterol in both the test and control groups of animals In some of the

Fig 5 Dog No 9 Small myocardial artery showing pyknosis of intimal nuclei and severe degeneration with vacuolization of the vessel media Extravasation of red blood cells and edema of perivascular tissue is present (Magnification ×450)

serum cholesterol showed an initial increase but this was not sustained There was no constant relationship between the levels of serum magnesium and the total concentrations of serum cholesterol (Figs 1 and 2)

Electrocardiograms Serial electrocardiograms in the magnesium deficient and control animals revealed the following information In both groups sinus tachycardia was usually present with a rate of 130 to 150 per minute There were no significant differences in the measurements of the P R Q T and QRS intervals in either group Although there was an extreme variability in the normal electrocardiograms of the control animals with the frequent occurrence of negative T waves especially in Leads III aV_L and occasionally in the V leads a higher degree of negativity of the T waves was found in the electrocardiograms of magnesium-deficient animals The only constant feature in the electrocardiograms of the magnesium deficient animals was the occurrence of the RST segment depression especially in the V leads associated with some flattening or inversion of T waves These changes were usually not related to the degree of hypomagnesemia since they did not appear until the marked deficiency had been present for many weeks or many months They were most often seen at the termination of the experiment (Fig 4) In some instances the appearance of the RST segment depressions and T waves were only of a transient nature Electrocardiograms taken at a later date while the animals were still hypomagnesemic showed isoelectric RST segments with the previously inverted T waves now upright In summary therefore although transient changes in the RST segment could be noted frequently in the magnesium deficient group there was no definite correlation in the electrocardiogram with the level of serum magnesium

Pathologic findings On gross examination the hearts of the magnesium deficient

Fig 6 Dog No 33 Myocardial vessel showing pronounced edema of the arterial media with large vacuolated cells Severe interstitial edema of the myocardium is present The veins are markedly congested (Magnification ×450)

Fig 7 Dog No 2 Cross section of a medium size coronary artery demonstrating degenerative changes in the thick vessel media with vacuolar degeneration and disorganization of the smooth muscle cell (Magnification ×4 0)

and control animals did not reveal any recognizable differences The weights configurations and outer surfaces appeared to be the same The endocardial surfaces of the hearts of a few of the test animals showed foci of subendocardial hemorrhage Grossly recognizable calcifications were not observed in any of the hearts In the intima of the aorta and the majority of the coronary vessels no atheromatous plaques or calcifications could be seen

On microscopic examination the control animals showed no significant pathologic changes in any of the sectioned organs Only the pathologic findings in the cardiovascular system of the test animals will be described in this paper and are as follows

The most significant finding was degenerative vascular change observed in various organs particularly in the heart They were readily recognized in arterioles and small arteries and involved the different layers of the vessel wall The intimal lining cells showed pyknosis or absence of their nuclei along parts of the circumference (Figs 5 7) An increase in the thickness of the intima or evidence of intimal proliferation was not found In the media of many vessels a loose arrangement of the smooth muscle cells was noted giving the impression of edema in this layer (Fig 7) Deposition of pink staining homogeneous material was observed in the media with more or less marked degeneration of the smooth cells up to complete necrosis of parts of the vessel circumference In some situations complete disintegration of the vessel occurred associated with extravasation of blood (Fig 8) Edema was also noted in the adventitia of the vessels which showed somewhat more pronounced changes (Fig 7)

Medium sized branches of coronary vessels did not exhibit such severe alteration of their walls Frequently however vacuolization of the smooth muscle fibers of the media was noted particularly in the outer

Fig 8 Dog No 9 Advanced degeneration of a myocardial vessel showing complete disintegration of the vessel wall along a portion of the circumference The extravasation of red and white blood cells marked with surrounding edema (Magnification ×2 0)

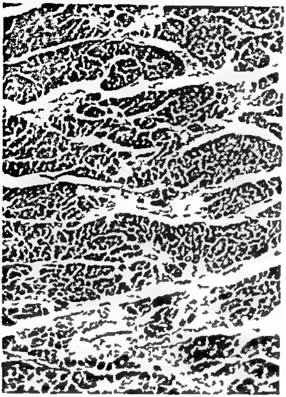

Fig 9 Dog No 6 Small fibrous scars are seen scattered through the myocardium representing old healed lesions (Magnification ×100)

one third of the media These vacuolated smooth cells had foamy cytoplasm with displacement of the nuclei to one side Some of the medium sized coronary vessels showed only a loose arrangement of the vessel wall with faintly pink staining material between the smooth muscle fibers suggestive of edema Increased deposition of collagenous fibers in the adventitia was frequently observed Intimal thickening was not found in the aortas or coronary vessels and in no situation was any deposition of calcific or atheromatous material observed Sudan black B stains in three of the heart sections were negative for deposition of fat in degenerated vessel walls

In the myocardium irregularly distributed small patches of hyperchromatic staining myocardial fibers were encountered This change was considered to represent the earliest stage of myocardial degeneration These small patches were most often seen about or adjacent to blood vessels which showed degenerative changes as described above In some of the heart sections frank myocardial necrosis was encountered with loss of nuclear staining in the heart muscle fibers In these situations infiltrations by polymorphs and extravasation of red blood cells was seen such as may be encountered in the usual myocardial infarct In addition to these fresh areas of myocardial damage older lesions were seen represented by patchy fibrous replacement of myocardial fibers (Fig 9) In only a few of the test animals were tiny plaques of calcification observed in small areas of recent myocardial necrosis or in young scars (Fig 10) The deposits of calcium were microscopic however and could not be identified upon gross examination The fresh as well as older lesions in the myocardium were generally small and irregularly distributed throughout the layers of heart muscle Very often old and recent lesions were found side by side both in the myocardium and in the vessels as well

Degenerative lesions were also encountered in the kidneys and other structures

Fig 10 Dog No 2 One of the small foci of calcification which were infrequently encountered in the myocardium (Magnification ×200 Van Kossa stain)

These changes will be described in full in a future communication ■

Discussion

Many of the manifestations of magnesium deficiency which have been described by others were regularly observed in the present experiment These include nutritive failure lack of growth characteristic changes in the paws skin lesions hyperirritability tetany and finally death

On the basis of the fact that the diet employed in this experiment was deficient only in magnesium and contained adequate amounts of all other nutritive constituents including minerals and vitamins and on the basis of the observation that the addition of the magnesium supplement to this deficient diet prevented the development of abnormal changes in control dogs one may assume that in all probability the clinical and pathologic alterations observed in our experimental animals are primarily the result of magnesium deficiency

Among various species marked differences as well as similarities have been noted in the pathologic changes in the heart and blood vessels in the presence of magnesium deficiency[1 24] In the main especially in rats the lesions described were those of focal areas of myocardial necrosis occasionally about small vessels with round cell infiltration with or without the addition of calcification A true calcinosis involving the diaphragm endocardium and intima of small blood vessels was observed in milk fed calves[15] More recently in studies on hypomagnesemic dogs Vitale and associates[27] reported histopathologic changes which consisted mainly of calcification of the elastica and media of the aorta and of coronary arteries and other peripheral arteries and of the inner portion of the myocardium In several of the coronary arteries a slight to moderate fibrous intimal reaction was noted in the form of plaques which were found to be fat free Syllm Rapoport and Strassburger[21] again reporting on dogs subjected to a magnesium deficient diet showed no calcification in the heart or blood vessels except when the dogs received additional calcium chloride by intravenous injection In a most recent study by Bunce and associates ■ gross aortic calcification was noted Microscopically the calcification was observed to occur in both the intimal and medial layers in association with hyalin degeneration and inflammatory necrotic changes Similar deposits were also noted in the carotid artery as well as other organs such as the kidneys and spleen However no such visible lesions were noted in the cardiac muscles of their animals

In the present study the intramyocardial vascular lesions described above were a constant finding in all of our animals in which significant hypomagnesemia had been attained and maintained under conditions of the experiments Lesions of similar character were not encountered in any of the control animals Such vascular changes have hitherto not been described in the hearts of dogs nor any other animals made hypomagnesemic

Because of the constancy of these vascular lesions in the heart as well as in other organs subsequently to be described it is assumed as probable that prolonged hypomagnesemia plays a part in producing degenerative changes in small myocardial vessels These changes include swelling and degeneration of the cells of the media swelling and even loss of some of the intimal lining cells together with edema and disorganization of the vessel walls which leads to a reduction in the caliber of the lumen and hence to a diminished flow of blood through such altered blood vessels At times segmental necrosis of portions of the wall of small vessels occurs Such degenerative vascular changes lead not only to a diminished flow of blood to a given portion of the myocardium but also to altered permeability and at times to extravasation of blood producing microscopic or even larger foci of myocardial necrosis which progress to fibrotic healing and/or to focal calcification Whether hypomagnesemia in addition acts directly upon the myocardial fibers by interfering with the mitochondrial activity[24 25] and thus leads to small foci of necrosis cannot be substantiated or excluded under the conditions of these experiments

It is interesting to note that the degree of calcification in the above mentioned experiments is generally less than tha

ported in dogs by other investigators[21,24] No foci of calcification in the intima of the aorta or large coronary arteries were observed in the present study Species variation and conflicting values have been reported concerning the levels of serum calcium and inorganic phosphorus with depression of serum magnesium[1,16,19,3] Although the levels of calcium in our dogs were slightly depressed in association with a slight elevation of serum inorganic phosphorus the animals in our experiments can in no way be said to have been hypocalcemic to a degree which would explain the lesser incidence of calcification in the myocardium and its absence in the aorta More recently Bunce and associates[3] reported gross calcific lesions in the aortas of their puppies with no visible lesions in the cardiac muscle in association with similarly depressed levels of serum calcium and slightly elevated levels of serum inorganic phosphorus

Whereas the causes of the differences in the experiments of induced pathology in dogs can only be conjectured upon there are certain factors which are known to affect the degree of magnesium deficiency Variations in dietary magnesium higher calcium phosphorus or higher fat and protein in the diet as well as the age of the animals may alter the severity of the magnesium deficiency syndromes[4,21,26,27] In the foregoing experiments the dogs at the onset of the experiment were somewhat older the amount of fat in the diet was higher and the amount of magnesium was extremely low which resulted in much lower levels of serum magnesium than reported by others[1,4]

In contrast to the findings reported by Syllm Rapoport[22] in electrocardiographic studies of dogs with experimental magnesium deficiency no definite pattern of electrocardiographic changes could be related to hypomagnesemia in the present study The only constant feature in the electrocardiograms of the magnesium-deficient dogs was the occurrence of the RST segment depression especially in the V leads associated with some flattening or inversion of the T waves These changes were not directly related to the levels of serum magnesium since they often did not appear until the animal had been markedly deficient for many weeks or many months and were most often seen at the termination of the experiment These electrocardiographic changes are interpreted therefore as being nonspecific in character and probably related to the underlying cardiac pathology already described above in the hypomagnesemic animals Fluctuation in electrocardiographic changes may be due to the development of the early and late lesions which have already been noted in the experimental animals

Conclusions

1 The external manifestations of magnesium deficiency previously described by others were regularly observed in the present experiments These include nutritive failure lack of growth characteristic changes in the paws loss of hair skin lesions hyperirritability tetany and finally death

2 The histopathologic changes consisted mainly of vascular degenerative lesions affecting the smaller radicles of the coronary arteries These vascular changes were associated with altered vascular permeability and at times with extravasation of blood leading to numerous foci of myocardial necrosis some of which terminated in fibrotic healing and/or focal calcification

3 The marked and prolonged lowering of the level of serum magnesium was associated with a slight elevation of serum inorganic phosphorus and slight depression of serum calcium but had no effect on the levels of serum sodium chloride potassium or cholesterol

4 Although transient RST segment and T wave changes were frequently noted in the magnesium deficient dogs there was no definite correlation in the electrocardiograms with the level of serum magnesium

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A simple chest electrode for orthogonal vectorcardiography

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Although there is now broad general agreement on the placement of electrodes for the derivation of the X (transverse) and Y (vertical) components of the orthogonal vectorcardiogram, there is still considerable divergence of opinion as to the most satisfactory method of determining the corresponding Z (anteroposterior) component for practical purposes.

The early geometrical Z leads of Duchosal and Sulzer,[1] Grishman, Borun, and Jaffe,[2] and Burch, Abildskov, and Cronvich[3] failed to satisfy the requirements of the lead field theory as propounded by McFee and Johnston,[4-6] who stated that in order to obtain a perfect sagittal lead "a system of multiple electrodes located on the left posterior chest behind the heart . . . and a similar set of electrodes on the precordium . . . will be required." Theoretically such a multiple unit should consist basically of an infinite number of minute electrodes connected in parallel, but in practice when a fairly small number of electrodes is used the resulting irregularities in the lead field through the heart will be negligible. Subsequently several authors[7-11] have recommended placements of electrodes based upon such a concept but having various numbers and types of skin contacts distributed in diverse configurations on the thorax and involving varying complexities of resistor networks.

Although most of these workers have suggested that their methods are relatively accurate and clinically practical, our experience confirms the opinion of McFee and Parungao[1] that some of these systems do not strike the optimum balance between accuracy and simplicity. Therefore these authors proposed a simpler technique requiring only 4 electrodes in the sagittal lead (3 anteriorly, 1 posteriorly) which they claimed represented a carefully drawn compromise between the simultaneous need to maximise accuracy and minimise complexity. However, when fewer individual small electrodes are used on the precordium their exact location becomes increasingly important and theoretically they should be disposed symmetrically in relation to the center of gravity of the ventricles. In practice this position is extremely difficult to determine.

Apart from the distribution of electrodes, another complication inherent in some systems has been the attempt to normalize the individual lead strengths as discussed by Schmitt and Simonson.[7] Such normalization has involved either the use of resistor networks to modify lead voltages or the varying of the amplification factors of the appropriate recording channels.

The simplified method as first described

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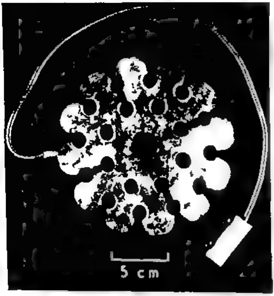

Fig 1 Tin disc chest electrode

by McFee[13] incorporated the use of a potentiometer in each lead to weight its strength in relation to the dimensions of the individual subject Nevertheless in the later account of the method McFee and Parungao[1] omitted the lead weighting factor and thereby made the sensitivity of their Z lead equal to that of X and Y since they concluded that the magnitude of the difference in lead strength from one individual to another was not great enough to justify custom tailoring of the leads to each subject

Another approach to the problem of simplification involves the employment of a single large electrode to cover the entire precordium with preferably a similar electrode placed posteriorly

In 1955 Helm[14] suggested an orthogonal system which utilized a large square stainless steel foil electrode held in place by a rubber strap and centered on the V position with a similar one posteriorly although he was of the opinion that the size of the back electrode was not critical At about the same time Reynolds and associates[8] discussed the possibility of using thin flexible metal plates and briefly reported some preliminary experiments but they were uncertain whether such electrodes would have uniform contact resistance over their entire surfaces

Although Helm[15] found the use of steel foil satisfactory he subsequently recommended[16] as more practical its replacement by a synthetic sponge sheet moistened with saline

Contemporaneously in this laboratory we were investigating the feasibility of replacing with a more malleable thin sheet of pure tin the 5-electrode chest unit then employed[10] As a result the type of electrode to be described below was evolved and has subsequently been subjected to exhaustive trial to prove its practical utility and reasonable accuracy

Method

The type of electrode is illustrated in Fig 1 It consists of a disc of pure tin 15 cm in diameter 0 5 mm in thickness fenestrated to allow of easy conformation to the thoracic surface thus ensuring uniform contact with the skin Sheet tin of this thickness is readily cut with scissors and the holes are easily punched out

After thorough application of electrode fluid to the precordium the anterior disc is centered over the heart moulded to the chest wall and held in place by a flat bag 16 cm square constructed from sheet polythene (approximately 0 025 mm thick) and containing 450 grams of silver sand An identical electrode in the corresponding posterior position is covered with a sheet of sponge rubber and retained in place by the

Fig 2 Representative planar loops

Table I. Mean planar and spatial vectorial data

			Mean planar					
			F $\hat{A}_{QRS}$	F $\hat{A}_T$	F $\hat{A}_{QRS-T}$	F $\hat{A}_G$	H $\hat{A}_{QRS}$	H $\hat{A}_T$
System utilizing disc electrodes			58	55	43	56°	314	63
		S.D.	18	10	19	10	39	13
Z lead electrodes	Retained by sandbag		58	53	45	55	336	61
		S.D.	22	10	22	11	52	15
	Tightly strapped		58	54	44	56	335	60
		S.D.	24	12	21	14	54	14
Significance of difference		t	0	0.45	0.48	0.57	0.48	0.50
		p		0.[illegible]	0.7	0.6	0.7	0.7

mvs. = Microvolt seconds.

weight of the body of the supine subject. If a viscous conducting paste is used, these electrodes are self-retaining even in the erect subject.

Normally, the differences in voltages which appear across this Z lead are recorded on a 4-channel Elema Mingograph Type 42 direct-writing electrocardiograph synchronously with those of the transverse and vertical leads previously described,[10] each lead having the same amplification factor.

The X lead consists of an electrode on each arm connected in parallel through 5 KΩ resistors with one placed on the thorax over the corresponding eighth rib in the anterior axillary line and the Y lead of a simple bipolar connection between the right side of the neck and the left leg.

Frontal, horizontal, and right sagittal planar loops were photographed on Kodak R 60 film from the screen of a Sanborn Vectorscope whose lead selector switch had been modified to permit the input of three independent bipolar leads. The electron beam was interrupted every 0.0025 second and the direction of inscription of each planar loop was indicated by the blunt ends of the tear-shaped light spots.

The methods used to derive the vectorial data and the nomenclature employed in their presentation are essentially those described in our previous publications,[10, 11] except for the manner in which the orthogonal lead axes have been designated. The earlier terminology in vectorcardiography, e.g., that of Grishman and Scherlis,[18] used the letters A, B, and C to label the transverse, anteroposterior, and vertical leads, respectively, and with this we originally conformed. However, more recently the use of the conventional solid geometrical terms X, Y, and Z for the three orthogonal leads has gained favor as being mathematically more acceptable, and in consequence this is the terminology which we shall employ in the future.

Results

The results of a preliminary survey using this simplified technique on 40 young normal male students are presented in Table I. For these subjects the anterior disc electrode was held in place by the standard sandbag, but in order to illustrate that the application of constricting straps to the thorax produced no significant alteration in vectorial values, a comparison on an additional 14 subjects is also presented. For this part of the investigation each individual lay supine on the posterior disc electrode under which two rubber straps were already positioned but allowed to hang free. After the three orthogonal leads were recorded utilizing the standard sandbag, the latter was removed and the

angles						Mean spatial angle and magnitudes			
H ∠QRS-T	H ∠T	S ∠QRS	S ∠T	S ∠QRS-T	S ∠G	(SP) ∠QRS-T	(SP) QRS (mvs.)	(SP) T (mvs.)	(SP) G (mvs.)
+109 48	41 18	127 30	36 14	+91 35	59 15	84 30	34 11	74 24	86 28
+85 56	48 19	111 35	36 14	+75 39	52 15	40 32	78 10	77 28	90 30
+86 55	45 27	116 37	37 13	+79 41	55 17	40 32	29 10	74 27	88 34
0 46 0 7	1 25 0 3	1 72 0 2	0 58 0 6	0 83 0 5	1 63 0 7	0	0 53 0 6	1 37 0 2	0 77 0 5

straps were tightened over the anterior electrode without disturbing the subject in any way and the recording was repeated

Typical planar loops from three individuals are shown in Fig. 2

Discussion

The 2 lead electrode system presented here has the paramount virtue of simplicity for routine use. However in the detailed investigation of relatively few subjects it might be possible to attain somewhat greater accuracy by designing orthogonal leads to allow for individual characteristics of body build and electrical inhomogeneity but the enormous increase in technical difficulty and time involved do not justify such an approach in the examination of large numbers

If in these circumstances lead weighting factors are neglected the large disc electrode also has much to recommend it on theoretical grounds since as Helm[16] has observed such an electrode would integrate the potential developed at all points

It is this integrated potential which is highly desirable. Ideally in order to establish a uniform lead field through the heart the component electrodes of such a Z lead should be identical and sufficiently large to encompass the total surface projection of the heart anteriorly and posteriorly. In practice it was found that for adults discs which were approximately 15 to 20 cm in diameter were the most convenient but proportionately smaller electrodes were more suitable for infants

The tin discs described are simply made in the laboratory and are easily moulded to the thorax of either male or female subjects even in the presence of bony deformities and good contact can be verified by the impression of the electrode left on the skin. The posterior electrode having no projections is almost imperceptible in use and in the severely ill person has the great advantage of being inserted between patient and bed with the minimum of disturbance

In contrast to most of the currently used systems of vectorcardiography which involve the use of constricting straps to retain the chest electrodes in position the sandbag utilized in the method here described leaves thoracic movement unhindered and thus eliminates another source of embarrassment to the invalid. Therefore in order to determine whether this simplification of technique has had any influence on the cardiac electrical phenomena as expressed in the orthogonal vectorcardiogram an analysis of results obtained with and without strapping has been made (Table I) from which it is apparent that no significant difference either in vectorial ...ntation or magnitude could be demo...

strated thus proving that the simpler procedure does not impair electrical contact

In conclusion it should be stated that a comprehensive statistical comparison between this new method and several of the existing nominally orthogonal vectorcardiographic techniques has been carried out and the results are to be published soon

Summary

A simple 7 lead for routine orthogonal vectorcardiography is described utilizing a pair of fenestrated tin disc electrodes Its advantages over existing methods are discussed and mean vectorial data are presented

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The use of citrate salts for testing digitalis-induced cardiac arrhythmias in the experimental animal

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The toxic effects of digitalis on the myocardium continues to be a formidable problem in the management of cardiac patients. Considerable evidence exists that the incidence of digitalis intoxication is increasing.[1] This is generally attributed to the concomitant use of saluretic drugs with the glycosides in the management of congestive heart failure, hypertension, and other edema states. The loss of potassium during diuresis makes the myocardium more sensitive to the toxic action of digitalis. Consequently, patients on a previously tolerated dose of digitalis may develop severe disturbances of cardiac rhythm and conduction. Digitalis toxic arrhythmias are often lethal.[1,4] Lown and Levine[3] have demonstrated a mortality rate as high as 65 per cent when supraventricular tachycardia with block results from digitalis intoxication. These high mortality figures and the increasing frequency of the disorder provide the stimulus for the discovery of better means of detecting and treating digitoxic cardiac arrhythmias. At present, digitalis intoxication may be treated by the administration of potassium[5,6] and by the use of calcium chelating agents.[7-11] In both of these methods an attempt is made to favorably influence the potassium-calcium ratio—in the one instance by augmenting depleted body and myocardial potassium stores by oral or careful intravenous potassium supplementation,[5,6] and in the other by lowering the level of ionized calcium in the serum.[14] The intravenous infusion of potassium is hazardous because it depresses A-V node and ventricular conduction and may cause ventricular standstill.[2,15,16] Therapy with oral potassium is slow in producing beneficial effects in established digitoxic arrhythmias. The use of chelating agents, such as the salts of EDTA (ethylenediaminetetraacetic acid), is also hazardous.[17] The most dangerous principal side effects have been the production of severe hypotension or hypocalcemic tetany. These agents also have been known to cause paraesthesia, nausea, vomiting, urinary frequency, myalgia, skin rash, histamine-like reactions consisting of nasal congestion, lacrimation, and frequent sneezing, and severe

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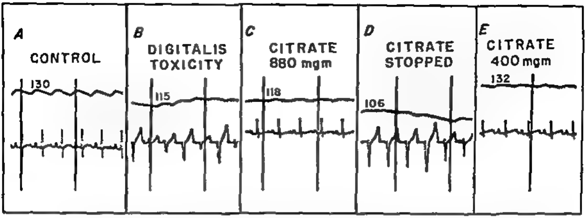

Fig. *1.* Demonstrates the effect of 4 per cent sodium citrate solution on digitalis toxic arrhythmia. The arterial blood pressure is recorded above the electrocardiogram in each photographic strip. Control tracing *A* was recorded and then digoxin was administered intravenously. Strip *B* demonstrates bizarre digitalis toxic arrhythmia with a slight drop in systemic pressure to 115 mm. Hg. *C*, Sodium citrate 880 mg. was administered intravenously. The rhythm converted to regular sinus rhythm within 4 minutes. In *D*, 10 minutes after the citrate was administered, ventricular tachycardia has recurred. The blood pressure dropped to a mean of 106 mm. Hg. In *E*, immediately after the administration of 400 mg. of sodium citrate, the rhythm again converted to regular sinus rhythm and the blood pressure increased to 132 mm. Hg.

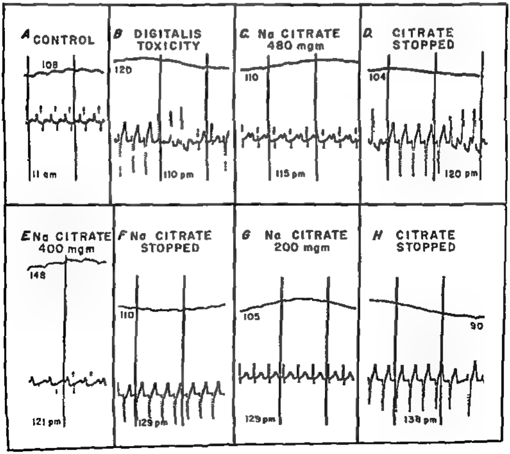

Fig. 2. (*For legend see bottom of opposite page.*)

side effects ranging from damage of the proximal renal tubular cells to local thrombophlebitis at the site of injection.[17] In a quest for other methods to alter the serum calcium ion, we recognized that sodium citrate might be considered a chelating agent in the biologic sense. Two series of experiments were carried out in the experimental animal to determine the effects of sodium citrate on digitoxic cardiac arrhythmias.

Procedure

Test Series A. Sixteen dogs were anesthetized with intravenous Pentothal sodium. Each animal then received repeated doses of intravenous digoxin until cardiac arrhythmias were established and maintained. The mean dose of digoxin necessary for this effect was 0.14 mg. per kilogram of body weight when given intravenously and 0.33 mg. per kilogram of body weight when given into the peritoneal cavity. This dose is four to five times the calculated dose per kilogram of body weight normally given to adult human beings. When the toxic arrhythmia had been well established for a period of 30 minutes, attempts were made to convert these arrhythmias by the intravenous administration of 4 per cent sodium citrate solution or acid citrate dextrose solution.* These solutions were administered intravenously to the dogs: *Group 1*—by repeated single dose injections (6 dogs); *Group 2*—single dose injections followed by drip infusion (3 dogs); and *Group 3*—continuous drip infusion only (7 dogs).

In 4 experiments, 10 per cent calcium chloride solution was given intravenously after the digoxin induced arrhythmias had been repeatedly converted by the citrate solution.

Test Series B. Supraventricular and ventricular cardiac arrhythmias were induced in 10 dogs by application of aconitine to the atria or ventricles. This experimental group was studied in order to determine whether 4 per cent sodium citrate solution would influence aconitine induced arrhythmias. After these rapid cardiac arrhythmias had become established for 30 to 60 minutes, large doses of citrate solution were given either by multiple repeated or single dose injections or by continuous intravenous infusion.

Results

The intravenous administration of 4 per cent sodium citrate solution or acid citrate-dextrose solution reverted the rapid complex digitoxic arrhythmias to a regular rhythm in each of the 16 dogs used in this series.

Series A. Group 1 (6 dogs). In the dogs treated by *intermittent* repeated injections of citrate solution, it was noted that initial doses of citrate ranging from 25 to 30 ml. when given rapidly over a period of 1 to 2 minutes could most effectively interrupt the arrhythmia (Figs. 1 and 2). Subsequent injections of smaller amounts of citrate solution (5 to 10 ml.) could convert the arrhythmias after the initial dosage. The duration of reversion was transient, varying from 1 to 5 minutes, but was more prolonged after several doses of citrate or if larger doses (20 to 25 c.c.) were given. In one experiment, after a total dose of 40 ml. of citrate solution given during two previous reversions, a subsequent dose of 10 ml. resulted in the re-establishment of a normal sinus rhythm that *persisted* for 29 minutes. In these experiments the dogs

* Baxter Travenol's anticoagulant solution B U.S.P. Each 100 ml. contains sodium citrate 1.3 Gm., anhydrous citric acid U.S.P. 0.44 Gm., hydrous dextrose U.S.P. 1.47 Gm.

Fig. 2. Demonstrates the effect of sodium citrate on digitalis-induced arrhythmia. The electrocardiogram is shown on the lower line and systemic blood pressure on the upper line. *A*, Control tracing at 11 A.M.; digoxin was administered. *B*, At 1:10 P.M., digitoxic cardiac arrhythmia. Sodium citrate was injected intravenously at 1:13 P.M. *C*, At 1:15 P.M. the arrhythmia converted to regular sinus rhythm. The citrate was stopped. *D*, At 1:20 P.M. the bizarre ventricular arrhythmia recurred. *E*, After 400 mg. of citrate had been injected, the rhythm converted to regular sinus rhythm. At 1:21 P.M. the blood pressure increased to a mean of 148 mm. Hg. Citrate was stopped and the ventricular tachycardia recurred at 1:29 P.M. (*F*). *G*, Sodium citrate, 200 mg., was injected intravenously and the rhythm converted. The citrate was then stopped and at 1:38 P.M. (*H*) the ventricular tachycardia recurred.

received large total doses (0 8 to 4 3 Gm of citrate) over short periods of time Cardiac asystole could be induced if excessive amounts of citrate were given

Series A Group 2 (3 dogs) After the initial reversion with an injection of 25 to 30 ml of 4 per cent sodium citrate solution these animals were placed on a drip infusion of the solution In 2 dogs it was possible to maintain normal regular rhythm with gradually decreasing rates of infusion and finally to discontinue the infusion altogether These animals survived the experiments having received a total of 8 to 12 Gm of citrate in 3 and 4 hours respectively In the other dog acid citrate dextrose solution was used Although a rapid reversion to normal rhythm was effected by an initial injection of 15 to 25 ml of this solution drip infusion could not satisfactorily maintain a regular rhythm

Series A Group 3 (7 dogs) A satisfactory reversion of the digitoxic arrhythmia could be obtained by starting treatment with a rapid drip infusion of 4 per cent citrate solution (42 to 300 drops per minute) until the rhythm reverted after which the infusion rate was gradually decreased to that which was just sufficient to maintain a regular rhythm (Fig 3) It was possible to discontinue the drip infusion in most instances and 6 of the 7 animals survived In this manner large total amounts of citrate (2 to 7 Gm) were administered during these experiments over periods of infusion which ranged from 1 to 3 hours The rate of infusion of citrate in these experiments varied from 0 2 to 6 3 mg per kilogram of body weight per minute

In one experiment sodium Versenate was administered to compare its effectiveness (Fig 4) The Versenate was not effective in terminating the arrhythmia despite a drop in systemic arterial pressure On the other hand an infusion of sodium citrate converted the rhythm repeatedly three times without a significant drop in arterial pressure

The rapid administration of large doses of citrate solution although relatively safe occasionally produced a moderate fall in the blood pressure in some animals and resulted in ventricular asystole after large total doses of citrate were used

The toxic arrhythmias could be instantly re established by the injection of 2 ml of 10 per cent calcium chloride solution after a normal rhythm had been established by the injection of sodium citrate It was possible to instantly induce or abolish the digitoxic rhythms by the alternate administration of 5 ml of sodium citrate solution and the calcium chloride solution

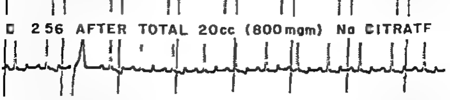

Fig 3 Demonstrates the effect of an intravenous drip of 4 per cent sodium citrate solution on a digitoxic rhythm (strip *A* at 2.28 P M) *B* After 15 c c of 4 per cent sodium citrate solution was administered at 156 drops per minute the rhythm converted to a bigeminal rhythm regular sinus rhythm with alternate frequent premature ventricular systoles In *C* at 2.56 P M after a total of 20 c c of citrate solution had been administered regular sinus rhythm had been restored

Series B It was not possible to revert the aconitine induced arrhythmias in any of the 10 dogs by any method of administration of the citrate solution

Discussion

The experiments clearly demonstrate that sodium citrate is able to correct digitalis induced cardiac arrhythmias This beneficial effect is probably due to the formation of a calcium citrate complex which is poorly dissociable thereby decreasing the ionized fraction of the serum calcium The reduction in the ionizable calcium renders the heart less sensitive to the digitalis In this respect its mode of action is similar to that of the salts of EDTA (ethylenediaminetetraacetic acid) *In a physiologic sense the salts of citric* acid act like a chelating agent

An optimum calcium potassium ratio *must* exist in the intracellular and extracellular fluid for normal heart action Calcium and potassium seem to have opposite effects on the heart and each to some extent can nullify the effects of the other Calcium acts in a way that is synergistic with digitalis and antagonistic to potassium in cardiac activity The calcium ion either inside or outside the myocardial cell membrane may alter the permeability *of the membrane to cation passage* The action of digitalis is probably due to its effect on the regulation of the concentration of potassium ion within the myocardial cell and calcium probably further influences the passage of potassium ions by altering the permeability of the cell membrane [18,19] Lowering the plasma calcium ion level appears to augment intramyocardial cellular potassium ion concentration which acts to decrease the irritability of the heart Conversely the administration of calcium or digitalis tends to lower intramyocardial potassium ion concentration by increasing the barrier to the reentry of potassium ion into the cell Thus it produces an increased cell irritability and predisposition to arrhythmia because of the decrease in potassium ion concentration A diseased myocardium tends to have a heightened sensitivity to digitalis is is frequently manifested by a toxic response to the average dose of this drug *It is possible that the beneficial effect which* citrate salts and other calcium binding agents have on digitalis induced arrhythmias is to change the cell membrane so that lowering of the plasma cation level augments the intramyocardial cellular potassium ion concentration This in turn acts to decrease the irritability of the heart muscle cell

Infused citrate rapidly disappears from *the plasma* as a result of (1) distribution throughout the extracellular space (2) excretion in the urine and (3) metabolic destruction Ludbrook and Wynn[20] have demonstrated a linear relationship between the rate of infusion of citrate and the rise *in the plasma* citrate level in normal man and in dogs For each 1 mg of citrate in

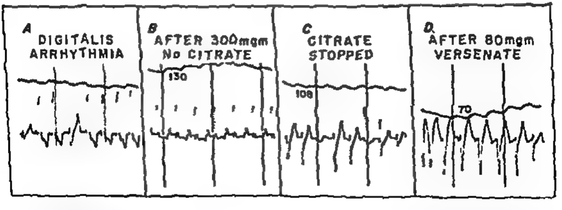

Fig 4 An arrhythmia was induced by administering a large dosage of digoxin (*A*) After 300 mg of sodium citrate was administered intravenously the rhythm converted to regular sinus rhythm (*B*) Fifteen minutes after citrate was stopped the arrhythmia returned (*C*) Versenate 80 mg failed to correct the arrhythmia but induced marked hypotension (*D*)

fused per kilogram of body weight per minute the serum citrate concentration rises by 20 mg per 100 ml in dogs and 12.5 mg per 100 ml in man. Studies on excretion have demonstrated that dogs will excrete 40 per cent of the infused citrate in the urine whereas man eliminates approximately 20 per cent by this route. The remainder is metabolized by the liver. Citrate metabolism may be abnormal in patients with severe liver or kidney dysfunction or during hypothermia or when there is mechanical obstruction of the hepatic circulation such as might occur with surgical occlusion of the portal vein or the thoracic duct.

The maximum rate at which citrate can be safely infused is not precisely known. Fatal cases of citrate intoxication have usually been the result of rapidly administered massive blood transfusions. Fatal cases have been reported as a result of infusion rates which varied from 5 to 10 mg per kilogram per minute up to 22 mg per kilogram per minute.[1-3] The decrease in the ionized fraction of the serum calcium levels during the infusion of citrate may cause tetany and convulsions, hypotension, or profound flaccidity of the myocardium. These effects can be reversed to some extent by the administration of calcium chloride. Extreme care is necessary, however, if the patient is digitalized because of the difficulty in estimating the amount of calcium required to restore adequate serum levels without inducing serious arrhythmias.

This study indicates that the beneficial effects which are due to the infusion of citrate are transient when the agent is given in intermittent injections. The duration of conversion of the digitoxic arrhythmias varied from 1 to 5 minutes, becoming more prolonged after several injections of the citrate solution. Our observations also demonstrated that the prolongation of the A-V conduction caused by the digitalis was not affected, but the complete A-V dissociation usually could be corrected. The Q-T interval became prolonged because of the hypocalcemia. Muscle tremors resembling tetany were frequently noted. Severe hypotension did not result unless massive doses of citrate were given rapidly or a large dose was injected after several doses of citrate had already been administered. In contrast, sodium Versenate requires a longer interval to produce an effect and is notorious for its hypotensive effect (Fig. 4). Survival was most frequent in those dogs in which the citrate was infused over a prolonged period.

Conclusion

The first step in the treatment of digitalis intoxication is the withdrawal of the digitalis preparation. If the effects of the digitalis toxic arrhythmia are mild, no further treatment is necessary, since the digitalis is excreted within a few days and the rhythm will correct itself. However, if the clinical condition of the patient or the type of arrhythmia is of a serious nature, other forms of treatment are necessary. The administration of potassium salts orally or by the intravenous route may correct the cardiac arrhythmia in a few hours or days. However, potassium should not be administered if the patient already has hyperkalemia due to renal damage or if the patient has depression of the A-V node causing a conduction defect. The administration of potassium under these circumstances is apt to induce other serious cardiac arrhythmias, and in case heart block already exists it will probably increase the degree of the block and result in Adams-Stokes syndrome or death. Quinidine, procaine amide, and vasopressor drugs have been used successfully in the treatment of ectopic arrhythmias due to digitalis toxicity.

If these measures fail, another approach to the treatment is the reduction of the free calcium ion in the serum with a chelating agent such as EDTA or citrate.[9-11] Because of its toxic effects there is a certain hazard in the use of sodium Versenate.[16,17] Also, sodium Versenate cannot be relied upon as a specific test of digitalis toxicity because arrhythmias other than those due to digitalis toxicity can also be corrected by the use of sodium Versenate.[16] Therefore, reliance on sodium Versenate as a test of digitalis toxicity in the presence of a false negative test could result in more serious digitalis toxicity because more digitalis might be administered. It would appear that the use of sodium citrate is a more effective way of demonstrating digi

talis toxicity, because only small amounts will correct the arrhythmia in just a few minutes

Hypotension and citrate toxicity do not occur with such small amounts The application of citrate in the treatment of human beings with digitalis toxic arrhythmias has not yet been made The citrate will probably have to be dripped slowly over a period of hours until the digitalis is excreted

Summary

Sodium citrate and acid citrate dextrose solution effectively correct digitalis induced arrhythmias in the dog It must be constantly administered to maintain normal rhythm This preliminary study would indicate that citrate may be used to test whether the arrhythmia is caused by digitalis and may prove to be an effective agent for the correction of digitalis toxic rhythms Citrate salts do not terminate cardiac arrhythmias due to aconitine

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Case reports

Right pulmonary artery-left atrial communication

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During the past 18 years rapid progress has been made in the surgical treatment of the patient with cyanotic congenital heart disease Since it is now possible to cure patients with many forms of cyanotic congenital heart disease it is imperative that the clinician accurately define the abnormal physiology producing the cyanosis prior to surgery In many cases this can be done on the basis of routine clinical x ray and electrocardiographic findings In other cases it is necessary to resort to the specialized procedures of cardiac catheterization and cineangiography before a definite conclusion can be reached

The purpose of this paper is to present the case of a 14-year old cyanotic boy in whom the findings on physical examination and in the electrocardiogram were normal and whose x ray films were interpreted as being normal Despite this he was symptomatic and moderately cyanotic and was ultimately proved to have an anomaly which was completely correctable

Case report

I F C (6 67 10) a 14 year old Negro boy entered Children s Hospital for the first time on July 12 1962 for evaluation of cyanosis

Present illness He was born of a full term uncomplicated pregnancy The birth weight was 9 pounds and 8 ounces and early growth and development were normal However cyanosis was noticed at birth and when he was 8 years of age clubbing of the fingers and toes first appeared Thereafter a slow but progressive increase in the cyanosis occurred Dyspnea on exertion and easy fatigability had appeared in recent months At no time had the child had nocturnal dyspnea syncopal attacks or squatting

Past illnesses The patient had had measles mumps pertussis varicella and scarlet fever as a child A tonsillectomy had been performed when he was 7 year old There had been no other serious illnesses accidents or operations

Family history The mother 33 years old and father 38 years old are living and well There are three sisters ages 6 months 2 years and 10 year who are all living and well The paternal grandfather died of dropsy age unknown The maternal grandmother had an enlarged heart and kidney disease and died at an unknown age There was no other history of cardiovascular disease in the family

Physical examination The patient was a well developed well nourished apparently healthy Negro boy who was 175 centimeter tall and weighed 56 kilograms The blood pressure was 120/84 mm Hg and the pulse was 90 per minute There was moderate cyanosis of the lips and nail beds of equal intensity in the upper and lower extremities The mucous membranes and the conjunctivae were moderately suffused and there was definite clubbing of the toes and finger No hemangiomata of the skin or mucous membranes were present and the pulses were all normal in character The heart was not enlarged and the sounds were of good quality There was a Grade 1 blowing systolic murmur audible at the upper left sternal border The second

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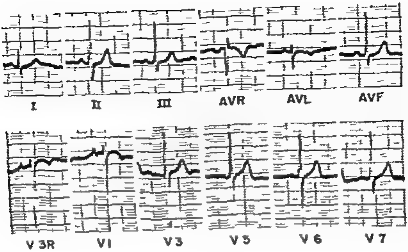

Fig *1* Normal electrocardiogram

sound at the base was normal in intensity and was normally split The lungs were clear and there were no abnormal masses or organs palpable in the abdomen Except for the clubbing and cyanosis the extremities were normal

Laboratory Hemoglobin was 20 6 Gm microhematocrit 69 white blood cell count 6 000 with normal differential Urinalysis was normal The tuberculin test (1 100) was negative

ECG The electrocardiogram (Fig 1) was within normal limits

X ray examination The chest was originally reported to be normal *(Fig 2) In retrospect* a rounded area of water density was noted in the left anterior oblique position just anterior to the barium filled esophagus (Fig 2 *D*) In the left lateral and posteroanterior positions (Figs 2 *B* and 4) the same oval area of water density was noted

Course Cardiac catheterization (Table 1) was performed Oxygen saturations were uniform but rather low throughout the chambers of the right side of the heart and in the pulmonary artery The pressures in the chambers on the right side were within normal limits The peripheral arterial oxygen saturation was reduced The pressures in the brachial artery were normal Indicator dilution curves (Fig 3) were obtained from various sites With injection into the right pulmonary artery and the left atrium the appearance times and the initial portion of the curves were very similar This finding suggested that most of the blood which entered the right pulmonary artery went rapidly through a fistulous connection into the left atrium A smaller secondary hump was noted in the right pulmonary artery curve and represented normal passage of a small amount of blood through the right upper and middle lobe pulmonary arterial branches The right middle lobe branch of the right pulmonary artery was probed and did not appear to take part in the fistulous connection but the catheter repeatedly passed into the left atrium from the right lower lobe pulmonary artery The indicator-dilution curves from the left pulmonary artery revealed a distortion of the upstroke but the rest of the curve was essentially normal This distortion of the upstroke represents rapid passage through the pulmonary circulation by spill-over into the right pulmonary artery *It could not represent* rapid passage through the small left upper lobe fistula since no distortion was noted on the left pulmonary artery curve obtained during occlusion of the fistula by the balloon catheter When the balloon catheter (Fig 4) was inserted into the fistula and distended until the fistula was occluded the arterial saturation rose to 95 per cent Indicator-dilution curves from the right pulmonary artery main pulmonary artery and left pulmonary artery (Fig 5) with the fistula closed were all normal and identical in appearance When the fistula was occluded the patient s color became normal When the occlusion was released the cyanosis again became quite evident

Cineangiograms with injection of radiopaque medium into the left pulmonary artery revealed a small upper lobe fistula with an otherwise normal left pulmonary artery and normal return through the pulmonary veins to the left side of the heart

Table I *Catheterization data*

Site	*Per cent saturation*	*Pressure (mm Hg)*
IVC	45	
RA low	40	
RA mid	42	
RA high	4?	
SVC	42	
RV	4?	16/0
MPA	40	16/8 (10)
RPA	40	
RBA	65	110/69(85)
RBA*	95	

*After fistula was occluded by balloon catheter

Fig. 4. An area of water density is easily visible in the lateral and left anterior oblique views (*B* and *D*). It is not seen in the right anterior oblique view (*C*) and it is only faintly visualized in the posteroanterior view (*A*).

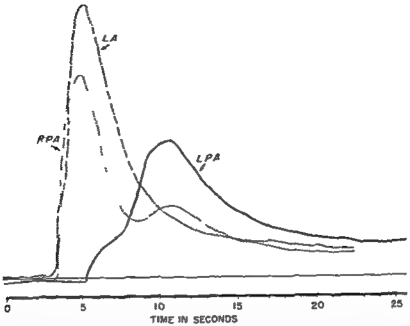

Fig 3 Indicator-dilution curves with fistula open The curves are labeled according to the site of injection All sampling was from the right brachial artery The curves suggest that most of the right pulmonary artery blood flow traverses the fistula See text for more complete discussion

Injection into the right pulmonary artery (Fig 6) showed branching into normal right upper lobe, right middle lobe and a small lower lobe vessel *In addition a huge lower branch proceeded medially* and inferiorly to the lower border of the right side of the heart where it formed an aneurysmal bulge which emptied into the left atrium

On Oct 2 1963 thoracotomy was carried out on the right side The right pulmonary artery and pulmonary vein were isolated Dissection of the right pulmonary artery revealed that this vessel bifurcated into a branch to the right upper lobe as well as one branch to the middle lobe There were three normal lobes on the right side Further distal dissection of the pulmonary artery disclosed that the branch to the right lower lobe also bifurcated into two branches The one branch was small and proceeded out into the lung The second branch larger and thinner walled was more medial and went directly into an aneurysmal bulge in the region of the left atrium This branch was doubly tied and closed by transfixing ligatures The digital cyanosis did not improve for several minutes after ligation but the mucous membrane showed an almost immediate improvement in color After the intrathoracic tube was positioned and the chest wall was closed the digits appeared to be normal in color The postoperative course was uneventful The patient was discharged on the twelfth postoperative day At that time his color was normal and his hematocrit had fallen to 46 An arterial oxygen saturation of 94 per cent was obtained *in a follow up out patient* visit in February 1963 (5 months postoperatively

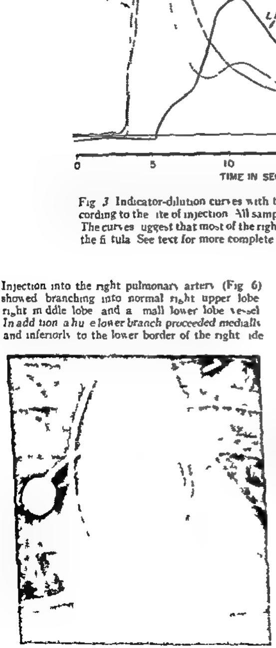

Fig 4 Spot film showing balloon catheter in the lower lobe branch of the right pulmonary artery The fistula is occluded by the inflated balloon

Discussion

In the differential diagnosis of cyanosis one must consider intracardiac disease pulmonary disease true polycythem

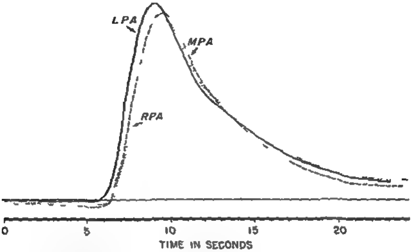

Fig. 5. Indicator dilution curves with fistula closed. Curves after injection into the main pulmonary artery (*MPA*), left pulmonary artery (*LPA*), and right pulmonary artery (*RPA*) are nearly identical.

monary arteriovenous fistula and anomalous systemic venous return. Our patient had exhibited normal growth and development and had only a very soft systolic murmur and a normal pulmonic second sound. He lacked electrocardiographic evidence of right ventricular hypertrophy and had a chest x-ray film which at first glance appeared to be normal. In view of the

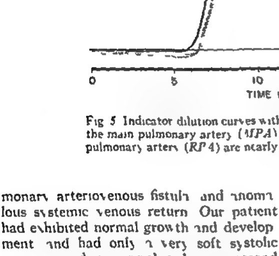

Fig. 6. Schematic drawing of the passage of contrast medium during selective cineangiocardiography. The tip of the catheter is directed into the right pulmonary artery, and the dotted line and arrows represent the course of the contrast medium through the right lower lobe branch of the right pulmonary artery, the fistulous tract, the left atrium, and the left ventricle.

foregoing findings it seemed unlikely that his cyanosis was due to an intracardiac lesion. There was nothing to suggest pulmonary disease. Polycythemia vera was excluded because of the normal white blood cell count and differential, the lack of splenic enlargement, and the marked degree of cyanosis and systemic arterial oxygen unsaturation. Our conclusion, therefore, was that he had either a pulmonary arteriovenous fistula or some anomaly of the systemic venous return to the left atrium. Many patients with pulmonary arteriovenous fistula have a continuous murmur, and most have abnormalities within the lung fields on x-ray examination.[1] Many have hemangiomata of the skin or mucous membranes. Since our patient had none of these, our tentative precatheterization diagnosis was anomalous systemic venous return to the left atrium. Such isolated systemic venous anomalies have been reported by Taussig,[2] Tuckman,[3] and Meadows[4] and associates.

This patient had a large right-to-left shunt from the pulmonary artery to the left atrium and no associated intracardiac anomaly. A review of the literature reveals 3 cases which are very similar to the one described. The first of these was reported by Taussig in 1947. The patient was a 15-year-old boy who had a direct communication between the right pulmonary artery and the left atrium, as well as a heman-

gioma on the forehead. He underwent successful surgical repair by Dr. A. Blalock. At examination 1 year postoperatively, he appeared to be perfectly normal; he had a normal blood count and an arterial saturation of 93 per cent.

The second case was reported by Castleman and Kibbee.[5] The patient was a 45 year old woman in whom the right pulmonary artery emptied into the left atrium. She had in addition hypertensive cardiovascular disease with myocardial infarction and cerebral embolism.

The third case was reported by Lucas and associates[6] in December 1961. The patient, a 3 year old white girl, had entered the hospital with convulsions and a left hemiplegia. A history of cyanosis from the age of 1 year had been obtained. She seemed to respond well to therapy and was discharged after 2 weeks. Approximately 3 weeks after discharge, she returned in a coma and died within about 6 hours. Postmortem examination revealed a brain abscess and a right pulmonary artery which emptied directly into the left atrium.

Lucas[6] has postulated that such pulmonary artery–left atrium communications are the result of agenesis of a lobe of the lung and consequent absence of the pulmonary capillary bed, with resultant communication between the pulmonary artery and pulmonary vein. Such an explanation seems to be untenable in our case in view of the three normal appearing lobes which comprised the right lung of our patient.

Although a pulmonary arteriovenous fistula, even when large, does not produce cardiac failure, it is a *definite threat* to the patient. The fistula may rupture since it has a very thin wall. These ruptures may vary from repeated minor episodes of hemoptysis to a single large fatal hemorrhage. The patient may suffer all the consequences of secondary polycythemia, as may any patient with cyanotic heart disease. Brain abscess may occur since, as in other forms of cyanotic congenital heart disease, venous blood bypasses the lung and enters directly into the systemic circulation. Lucas' patient[6] succumbed to a brain abscess, and Muir[7] has reported 5 cases of brain abscess in patients with pulmonary arteriovenous fistula. For these reasons, it is imperative that the lesion be corrected if it is found to be single, as in Taussig's case, or even if associated with a very minor fistula in the opposite lung, as in our own case.

From our cineangiograms and catheterization studies, it was quite evident that a large volume of blood traversed the fistulous tract. We estimated this to be about 55 per cent of right ventricular output. The studies of Friedlich and associates[3] have shown that the resistance of a fistulous tract is usually the same as that of a normal lung, whereas the resistance of the nonfistulous part of the pulmonary vascular system is about twice normal. The large flow through the fistula is therefore not surprising. The resulting normal peripheral arterial oxygen saturation after occlusion of the anomalous communication by the balloon catheter demonstrated the minor importance of the small left upper lobe fistula and justified surgical repair.

Summary

This 14 year old boy had an abnormal vascular connection which permitted a large right to left shunt, resulting in marked peripheral unsaturation, clubbing, and secondary polycythemia. Only recently had symptoms appeared, and with the exception of cyanosis and clubbing, his physical examination was normal. He had a normal electrocardiogram and only in retrospect was an abnormality noted on the chest x-ray film. The feasibility of surgical repair was demonstrated by occluding the anomalous right pulmonary artery–left atrial communication with a balloon catheter. Surgical repair has been performed with excellent results.

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Clinical, hemodynamic, electrocardiographic, and vectorcardiographic observations in progressive muscular dystrophy of 34 years' duration

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Pathologic findings in the myocardium similar to those within skeletal muscle have been described in patients with progressive muscular dystrophy.[1,2] A variety of electrocardiographic changes have been reported in patients with this disease, including tachycardia, arrhythmias, disturbances in conduction, and evidence of myocardial damage.[3-5] Abnormally deep Q waves in Leads I, aV_L, and V_6 and tall R waves in Lead V_1 in patients with pseudohypertrophic muscular dystrophy may be of value in differentiating these patients from those with facioscapulohumeral dystrophy.[5] It has also been suggested that the electrocardiogram may aid in distinguishing the sex-linked from the nonsex-linked patterns of inheritance in childhood dystrophy.[6]

A group of 12 patients with muscular dystrophy in various stages of development and without overt symptoms of cardiac failure were studied with right heart catheterization techniques by Gailani, Danowski, and Fisher.[7] Most of the patients had electrocardiographic abnormalities. The hemodynamic findings were normal at rest, but on exercise some of the patients developed changes consistent with congestive heart failure. This suggested that the absence of clinical failure might be related to the limited ability of the patients to exert themselves. Although overt congestive heart failure is reported in patients with muscular dystrophy,[3,4,8,9] a review of the literature reveals scant hemodynamic information during this period of the disease.[10,11] Patients with the myotonic form of the disease[12] are excluded from the present discussion.

The following case report describes a patient with progressive muscular dystrophy and cardiac involvement. Chest x-ray films and electrocardiograms were described and were available during the 34 year course of his disease, and hemodynamic observations were made at cardiac catheterization while he was in congestive heart failure. Vectorcardiographic studies not previously reported in these patients were also obtained.

Case report

The patient is a 47-year-old white male of Italian descent with no family history of neuromuscular disorders. In 1939, at the age of 23 years, he was hospitalized for slowly progressive bilateral weakness of the lower extremities, particularly noted on climbing stairs. This had first become apparent in 1929 after an operation for a ruptured appendix. No cardiovascular symptoms were present. On

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Fig 1A Chest film (photofluorogram) taken in October 1948 Heart size is normal with a slightly excessive convexity to the left border The right diaphragm is elevated

Fig 1B Chest film (photofluorogram) taken in October 1958 The heart size has increased particularly in the region of the left ventricle

physical examination there was atrophy and weakness bilaterally of the quadriceps muscles enlarged rubbery calf muscles and a positive Gowers sign The blood pressure was 107/60 mm Hg and the heart rate was 70 beats per minute with a regular rhythm The pulmonic component of the second heart sound was louder than the aortic component and no cardiac murmurs were heard Hematocrit glucose tolerance test circulation time venous pressure vital capacity electrocardiogram and chest x ray films were reported to be normal A low creatinine excretion of 1 14 Gm per 24 hours and an elevated creatine excretion of 0 32 Gm per 24 hours were obtained The diagnosis of pseudohypertrophic muscular dystrophy was confirmed by a biopsy of calf muscle which showed edematous and enlarged muscle bundles with fatty infiltration

The following year the patient was hospitalized again for additional diagnostic workup having been on various medications with no change in his symptom Physical examination was unchanged except for the possible appearance of enlargement of the deltoid muscle Over the next 18 years the patient remained asymptomatic aside from slowly progressive weakness of the muscles of the lower extremities and the shoulders This weakness did not handicap him severely except when he climbed stairs or inclines An x ray film of the chest taken in 1948 revealed a slight abnormality of the cardiac contour (Fig 1A) whereas the cardiac findings on physical examination were unchanged from those previously described

In October 1958 hospitalization was recommended for further evaluation because of the progression of his muscular disease In addition the patient had complained of *occasional palpitations* Physical examination showed a broad based gait a positive Gowers sign and weakness of all four extremities A biopsy of triceps muscle again was consistent with pseudohypertrophic muscular dystrophy The blood pressure was 110/80 mm Hg and the heart rate was 80 beats per minute The pulmonic component of the second heart sound was louder than the aortic component and there were no cardiac murmurs X ray examination of the chest revealed enlargement of the heart (Fig 1B) An electrocardiogram (Fig 2) revealed normal sinus *rhythm of 80 beats per minute P R interval of 0 14* second QRS duration of 0 13 second with left axis deviation small q waves and inverted T waves in Lead I and aVL and increased QRS voltage in the limb lead These findings were interpreted as showing intraventricular block and satisfying the voltage criteria for left ventricular hypertrophy

In 1960 the patient complained of mild exertional dyspnea X ray and fluoroscopic examination of the chest revealed further enlargement of the heart with enlargement of the left atrium and both ventricles and engorgement of the pulmonary arteries (Fig 1C) The heart rate was 120 beats per minute and regular and the blood pressure was 110/60 mm Hg A gallop rhythm was heard and the lung fields were clear to auscultation On digitalization the dyspnea and palpitations improved and the heart rate slowed

This improvement was maintained until December 1962 when he was rehospitalized for increasing exertional dyspnea paroxysmal nocturnal dyspnea orthopnea and cough of 2 month *duration* There were no complaints of chest pain at any time On physical examination the blood pressure was 160/90 mm Hg the heart rate was 110 beats per minute and persistent fine râles were present at both lung bases There was paradoxical splitting *of* the second heart sound at the pulmonic area a gallop rhythm and a Grade 2 systolic murmur at the

Fig *1C* Chest film taken in November 1960 Generalized cardiac enlargement has occurred

Fig *1D* Chest film taken in December 1962 Further generalized cardiac enlargement is seen at the time of hospitalization for congestive heart failure

apex The liver was not enlarged there was no peripheral edema and the neck veins were not distended Examination of the musculoskeletal system revealed the typical findings of pseudohypertrophic muscular dystrophy There was no myotonia and neurological examination was within normal limits except for those findings associated with muscular weakness

Laboratory data including hematocrit white blood cell count serum protein electrophoresis blood urea nitrogen serum electrolytes calcium phosphorus serum glutamic oxaloacetic transaminase lactic dehydrogenase protein bound iodine fasting blood sugar and cholesterol were normal The arm to tongue circulation time (Decholin) was 30 second Chest x ray examination showed further enlargement of the heart (Fig *1D*) An electrocardiogram (Fig 2 *Dec 1962*) revealed sinus tachycardia of 108 beats per minute P R interval of 0 18 second QRS duration of 0 13 second with left axis deviation decreased amplitude of the q wave in Lead 1 and disappearance of the q wave in Lead aVL inverted T waves in Leads I and aVL S T segment depression in Lead 1 aVL and V V and appearance of a QR pattern in Lead V These findings were interpreted as being consistent with an intraventricular block resembling a left bundle branch block pattern in the limb leads and right bundle branch block pattern in precordial lead The S-T changes might have been due in part to digitalis effect Treatment for congestive heart failure consisted of adjustment of the digitalis dosage restriction of salt and mercurial and thiazide diuretics This resulted in a 13 pound diuresis symptomatic improvement and return of the heart size toward that which existed prior to the onset of clinical congestive heart failure (Fig *1E*)

Three weeks later during which time the improvement in his cardiorespiratory status had been maintained right heart catheterization was performed The right ventricular end-diastolic pressure was normal the mean pulmonary arterial and pulmonary wedge pressures were elevated and the cardiac output was within the lower range of normal In addition to the data presented in Table 1 a left-to-right shunt was ruled out with the use of the platinum tipped hydrogen-sensitive electrode Vital capacity at the time was 2 8 liters 75 per cent of

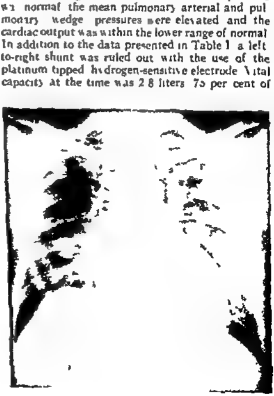

Fig *1E* Chest film taken in January 1963 after treatment for congestive heart failure The heart size and contour are now similar to that seen in 1960 (Fig *1C*)

Fig. 1A. Chest film (photofluorogram) taken in October 1948. Heart size is normal, with a slightly excessive convexity to the left border. The right diaphragm is elevated.

Fig. 1B. Chest film (photofluorogram) taken in October 1958. The heart size has increased, particularly in the region of the left ventricle.

physical examination there was atrophy and weakness bilaterally of the quadriceps muscles, enlarged rubbery calf muscles, and a positive Gowers sign. The blood pressure was 107/60 mm. Hg and the heart rate was 70 beats per minute with a regular rhythm. The pulmonic component of the second heart sound was louder than the aortic component, and no cardiac murmurs were heard. Hematocrit, glucose tolerance test, circulation time, venous pressure, vital capacity, electrocardiogram, and chest x-ray films were reported to be normal. A low creatinine excretion of 1.14 Gm. per 24 hours and an elevated creatine excretion of 0.32 Gm. per 24 hours were obtained. The diagnosis of pseudohypertrophic muscular dystrophy was confirmed by a biopsy of calf muscle which showed edematous and enlarged muscle bundles with fatty infiltration.

The following year the patient was hospitalized again for additional diagnostic workup, having been on various medications with no change in his symptoms. Physical examination was unchanged except for the possible appearance of enlargement of the deltoid muscles. Over the next 18 years the patient remained asymptomatic, aside from slowly progressive weakness of the muscles of the lower extremities and the shoulders. This weakness did not handicap him severely, except when he climbed stairs or inclines. An x-ray film of the chest taken in 1948 revealed a slight abnormality of the cardiac contour (Fig. 1A), whereas the cardiac findings on physical examination were unchanged from those previously described.

In October, 1958, hospitalization was recommended for further evaluation because of the progression of his muscular disease. In addition, the patient had complained of occasional palpitations. Physical examination showed a broad-based gait, a positive Gowers sign, and weakness of all four extremities. A biopsy of triceps muscle again was consistent with pseudohypertrophic muscular dystrophy. The blood pressure was 110/80 mm. Hg and the heart rate was 80 beats per minute. The pulmonic component of the second heart sound was louder than the aortic component, and there were no cardiac murmurs. X-ray examination of the chest revealed enlargement of the heart (Fig. 1B). An electrocardiogram (Fig. 2) revealed normal sinus rhythm of 80 beats per minute, P-R interval of 0.14 second, QRS duration of 0.13 second with left axis deviation, small q wave and inverted T waves in Lead I and aVL, and increased QRS voltage in the limb leads. These findings were interpreted as showing intraventricular block and satisfying the voltage criteria for left ventricular hypertrophy.

In 1960, the patient complained of mild exertional dyspnea. X-ray and fluoroscopic examination of the chest revealed further enlargement of the heart, with enlargement of the left atrium and both ventricles and engorgement of the pulmonary arteries (Fig. 1C). The heart rate was 120 beats per minute and regular, and the blood pressure was 110/60 mm. Hg. A gallop rhythm was heard, and the lung fields were clear to auscultation. On digitalization, the dyspnea and palpitations improved and the heart rate slowed.

This improvement was maintained until December, 1962, when he was rehospitalized for increasing exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and cough of 2 months' duration. There were no complaints of chest pain at any time. On physical examination, the blood pressure was 160/90 mm. Hg, the heart rate was 110 beats per minute, and persistent fine rales were present at both lung bases. There was paradoxical splitting of the second heart sound at the pulmonic area, a gallop rhythm, and a Grade 2 systolic murmur at the

tained his improvement on standard therapy of a reduced intake of salt digitalis and diuretics

The marked electrocardiographic abnormalities indicated considerable involvement of the myocardium The cardiac catheterization data established the presence of left ventricular failure It would seem reasonable to suggest that with electrocardiographic abnormalities of this severe degree in muscular dystrophy the likelihood of developing congestive heart failure is increased

Of interest is the sequence of events with reference to the cardiorespiratory system in this patient with progressive muscular dystrophy of 34 years duration The dystrophic involvement of the extremities appeared during adolescence followed 19 years later by early x ray changes in heart contour and 29 years later by marked abnormalities in heart size and the electrocardiogram The latter abnormalities preceded the development of overt congestive heart failure by 2 years although the possibility that subclinical failure existed prior to this time cannot be excluded In addition only the cardiac manifestations of his muscular dystrophy showed progression during these last few years This is in agreement with the pathologic finding that the duration and severity of the skeletal muscle disease seemed to bear no relationship to the severity of the myocardial disease[1]

Summary

A 47 year old man with proven muscular dystrophy was observed closely for 24 years after the initial diagnosis of his disease X ray films and electrocardiograms during this period revealed progressive abnormalities prior to the onset of the first clinical manifestations of congestive heart failure when he was 43 years old During the period of congestive heart failure catheterization of the right side of the heart revealed left ventricular failure A vectorcardiogram confirmed the scalar electrocardiographic findings of severe widespread myocardial disease The sequence of clinical events in the 34 year course of this patient s disease with particular attention directed to the cardiac manifestations is described

Addendum

The patient continued to do well for the next 6 months At the end of that time he was rehospitalized because of the sudden onset of pain in the right shoulder nausea vomiting cough with blood tinged sputum and pain in both lumbar areas There were no signs of congestive heart failure and a chest x ray film and electrocardiogram were unchanged from the previous admission Five days later he rapidly developed congestive heart failure with tachycardia distended neck veins basilar lung rales and peripheral edema A chest x ray film showed mild congestive changes An electrocardiogram revealed sinus tachycardia of 130 beats per minute with first degree A V block and nodal and ventricular premature beats Additional diuretic therapy with supplemental oral potassium was started with a good response Two days later the patient suddenly died in bed

At postmortem examination the heart weighed 560 grams with no gross evidence of a myocardial infarction The coronary arteries were patent with rare atherosclerotic plaques There were no congenital abnormalities or valvular lesions The thickness of the wall of the left ventricle measured 2 0 cm at the base and 0 8 cm at the apex the thickness of the wall of the right ventricle was 0 8 cm There was some interstitial myocardial fibrosis with focal areas of myocardial degeneration and lymphocytic infiltration Atherosclerotic changes were present in the pulmonary arteries and to a mild degree in the aorta The right and left lungs which weighed 710 and 560 grams respectively showed pulmonary edema and chronic passive congestion without primary lung pathology The liver and spleen showed long standing changes of chronic passive congestion Healed and recent infarcts of the kidneys were present The color of skeletal muscle from the area of the gluteal and shoulder regions was yellow and that from the upper leg was reddish brown The microscopic appearance of the muscle was consistent with the diagnosis of pseudohypertrophic muscular dystrophy

The autopsy findings excluded the more common forms of heart disease and were consistent with the type of cardiac involvement found in pseudohypertrophic

Clinical pathologic conference

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Clinical abstract

DR. HEATH: A 57 year old man while at a dinner on July 9 had difficulty in swallowing a small hard piece of potato and felt a sudden severe pain in the middle of the sternum. He took some antacid tablets, but these did not relieve his symptoms. He drove home and went to bed feeling somewhat apprehensive as he had suddenly become short of breath for no apparent reason. His previous health had been good. The following day the pain persisted and extended into the epigastric region. It was aggravated by movement, particularly when he moved onto his left side.

On July 11 he was admitted to hospital. On examination he looked pale and was sweating profusely. He vomited. He complained of pain in the upper abdomen and there was tenderness on palpation with guarding in the epigastrium and over the liver. The apex beat was impalpable. A loud harsh systolic murmur was heard over the middle of the sternum and this was conducted into the aortic area. His pulse rate varied between 100 and 120 per minute and his blood pressure was 130/75 mm. Hg. There were no adventitious sounds in the chest at this time.

On July 12 he still complained of pain in the upper abdomen.

Three days after admission to hospital, on July 14, he was still gravely ill. His skin had become cold and clammy and showed a faint cyanotic tinge. At 8:00 P.M. his blood pressure was recorded as 150/30 mm. Hg and he was found to have a collapsing pulse. Prominent pulsation of the neck veins was noted. There were rales and crepitations at the bases of both lungs.

On the following day his blood pressure had fallen to 70/30 mm. Hg and his radial pulse was barely perceptible. He was very cold and his breathing was stertorous. The murmur was no longer audible. He was still in severe pain.

He died on July 16.

Investigations. His temperature was 98.0° F. on July 11. It rose to a maximum of 99.5° F. on July 13 and then subsided to 97° F. on July 16.

Urine: specific gravity 1.027, reaction acid, sugar trace; blood, protein, acetone, and pus all negative.

Blood: hemoglobin 13.6 Gm. per cent (92 per cent); red cells appeared normal; white blood cell count 6,400 per cubic millimeter; normal differential; erythrocyte sedimentation rate 22 mm. in first hour (Wintrobe).

Serum amylase: 67 Wohlgemuth units.

Discussion

PROF. BLACKBURN: The first thing that obviously suggests itself is that this man had perforated his esophagus on swallowing a hard piece of potato. The fact that the pain persisted and moved into the epigastrium and was aggravated by movement is consistent with this diagnosis. I note, however, that there was no previous history of dyspepsia and it is likely that he merely accepted the mentioned antacid tablets from a friend at the dinner. This absence of previous symptoms led me to further consideration and I am now rather against this diagnosis since it seems to me that a small foreign body of this nature would not perforate an esophagus undamaged by previous disease. Further more, there was no history of associated vomiting such as one would expect if the esophagus had in fact ruptured. The elevation of his temperature was small and not at all like the high fever one would antici

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pate finding after mediastinitis secondary to perforation of the esophagus For such reasons I began to think it more likely that he had achalasia or even dysrhythmia of the esophageal muscle secondary to some other acute medical condition We are told that he went home and felt short of breath the pain in the chest continuing This combination of symptoms might be due to a pneumothorax complicating perforation of the esophagus but it seems to me that this is making rather a lot of a small piece of potato!

Since we are dealing with a middle aged man with chest pain we must consider of course a myocardial infarction which might be associated with both dysphagia and shortness of breath due to acute left ventricular failure However the reported sudden onset of a loud systolic murmur over the sternum is rather odd for a myocardial infarction because there does not seem to have been sufficient time before his death for the development of a complication of such a nature as might have given a murmur of this type It is conceivable that he had an infarction in an unusual site

Dissecting aneurysm of the aorta has to be considered because all the clinical findings are consistent with such a diagnosis Was this man abnormally tall and thin

DR HEATH You are obviously thinking of Marfan s syndrome No he was not of that build

PROF BLACKBURN In connection with his stature I am rather bothered about his impalpable apex beat Was he obese

DR SPENCER He was a heavily built man

PROF BLACKBURN Perhaps he had a pericardial effusion which masked the apex beat Presumably the murmur described is not meant to indicate a pericardial friction rub A systolic murmur is certainly consistent with a dissecting aneurysm but I should have expected it to be conducted down the sternum and not toward the aortic area It is also worth pointing out that this man was not hypertensive which does not exclude a dissecting aneurysm of the aorta but is one point a little against this diagnosis if he did not have Marfan s syndrome

Now I should like to deal with the important finding that at 9 00 P M on July 14 his systemic blood pressure changed dramatically and was recorded as 150 30 mm Hg and was associated with a collapsing pulse To explain this we might consider that the dissection was back and that he developed aortic incompetence Another possible explanation is that some systemic vessel has ruptured into a large vein or an atrium such as the rupture of a sinus of Valsalva into the right side of the heart In such conditions I should have expected to hear a diastolic murmur but this is not recorded as being present It is possible I suppose that such a murmur was present but missed on examination

In summary then I think that this condition is a cardiac one and I think it most likely that the diagnosis is one of dissecting aneurysm of the aorta with development of secondary aortic incompetence A ruptured sinus of Valsalva must also be borne in mind I should like to see a radiograph of the chest and an electrocardiogram

DR HEATH A radiograph was not taken in this case since the patient was considered to be too ill to cooperate but we have two electrocardiograms—one taken on July 12 and the other on July 15 Perhaps Dr Harris would like to comment on them

DR HARRIS I should like to make it clear that I am not an expert on electrocardiography! However right away we can say that the first ECG (Fig 1) shows no evidence of myocardial infarction The standard leads are normal except for an inverted T wave in Lead III which is within normal limits The unipolar and precordial leads are also within normal limits Perhaps the S T phase is a little abnormal and the T waves are of low voltage

PROF BLACKBURN But you would say that there is no electrocardiographic support for a diagnosis of myocardial infarction or pericarditis?

DR HARRIS Yes that is correct With regard to the second ECG of July 15 (Fig 2) the T wave in Standard Lead III is a bit lower but it is still within normal limits There is a small Q wave in Standard Lead III but again this is normal like the unipolar and precordial leads I strongly suspect that Lead V₃ has been shown upside down and the wrong way round but that only feature of ... importance

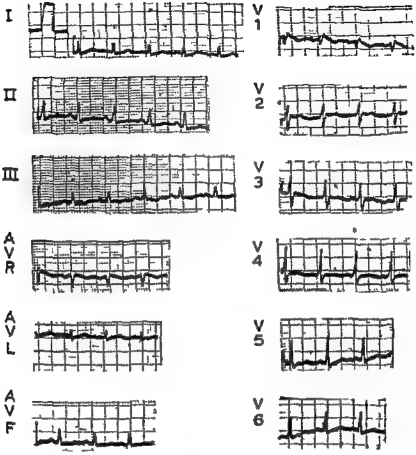

Fig *1* Electrocardiogram taken on July 12

PROF ARNOTT Professor Blackburn would you like to add to your summary that the dissection and rupture were intrapericardial

PROF BLACKBURN As a terminal phenomenon yes but I do not think that had his aorta ruptured into the pericardial sac he would have survived for [illegible] days with cardiac tamponade

PROF ARNOTT A ruptured aortic cusp would explain the high pulse pressure

MR ABRAMS (thoracic surgeon) Although I agree with the general conclusions reached by Professor Blackburn I do not agree that a small piece of hard potato could not cause perforation of the esophagus I have seen two cases of rupture due in one case to a mouthful of chop and peas and in the other to a piece of steak without garnishing Neither of these patients vomited and in both instances the diagnoses were not made for 3 days although fortunately both patients survived operation Also it is possible to have a peculiar dysrhythmia of the lower esophagus due to a relatively small bolus of food

PROF BLACKBURN I note that you say a mouthful of food I still think that perforation is usually due to a large bolus

DR HARRIS Professor Blackburn obviously has no experience of our Birmingham potatoes and not apparently of our Birmingham citizens for many of them have chronic bronchitis and emphysema and I think that these associated lung diseases may account for the impalpable apex beat that worried him so much

MR POURGOURIDES Had he chronic bronchitis in fact?

DR SPENCER He was a Birmingham citizen! But there was no macroscopic evidence of emphysema

DR HEATH I think that it is highly likely that in this case a diastolic murmur was also present in the region of the sternum

MR STEPHENSON If this were so it would

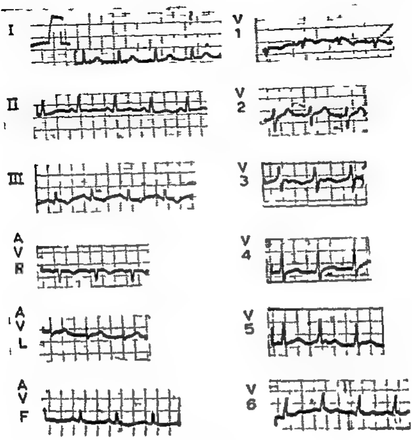

Fig 2 Electrocardiogram taken on July 15

seem likely that a rupture of an aneurysm of a sinus of Valsalva with survival for a number of days would be applicable in this case

PROF BLACKBURN Yes I included this possibility as a terminal phenomenon in this case It would explain many of the clinical features including the prominent pulsation of the neck veins It seems possible that rupture occurred into the right atrium

DR HEATH Perhaps at this stage we might ask Dr Spencer to tell us what he found at autopsy

DR SPENCER At this point we can assure Professor Blackburn that the piece of potato was in fact a red herring

At necropsy the body was that of a well built man The main pathologic features were confined to the cardiovascular system The pericardium was normal and there was no evidence of pericardial effusion or hemopericardium The heart was lightly enlarged and weighed 360 grams The walls of the ventricles were of normal thickness (right 0 3 cm left 1 3 cm) The myocardium appeared macroscopically to be normal and this was substantiated on histologic examination Apart from a tiny fenestration of the noncoronary cusp of the aortic valve all the cardiac valves were normal in structure and their circumferences were within normal limits

There was an opening 1 0 by 0 5 cm in the wall of the aorta immediately distal to the valve ring deep down behind the noncoronary cusp (Fig 3) This communicated with a thin walled sac 1 0 cm in diameter which protruded into the right atrium immediately above the commissure of the septal and anterior cusps of the tricuspid valve (Fig 4) An irregular tear was present in the wall of the sac The appearances were those of a rupture of an aneurysm of a sinus of Valsalva into the ri

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Fig 4 View from the right si l of the h art howing the protru ion of the aneurs m al ove the commi ure of th septal and anteri r cu p of the tricu pi l valve

There was severe confluent atheroma of both coronary arteries which were narrowed in several places but there was no evidence of thrombosis or a complete occlusion

There was slight atheroma only of the arch of the aort a but atheroma was more advanced in the abdominal region

A section through the heart in this case (Fig 5) shows the relationship of the aneurysm of the sinus of Valsalva to the noncoronary aortic cusp and the leaflets of the tricuspid valve The aortic media is separated from the aortic ring and only a few elastic fibers are visible in this intervening thin wall of the aneurysm The point of rupture is seen on the upper aspect of the aneurysm as it projects into the right atrium (Fig 5)

We may compare this with a similar section from a normal heart (Fig 6) Note the proximity of the bundle of His so that a large aneurysm of the sinus of Valsalva may affect the conducting mechanism and give rise to heart block or arrhythmias

The thin fibrous wall of the aneurysm (Fig 7) has numerous cardiac histiocytes within it There is no evidence of an acute inflammatory lesion or the vegetations of endocarditis

DR. HEATH Do you think that this aneurysm is a congenital abnormality?

Fig 5 Section through the aneurysm The arrow indicates the point of rupture The h avily stained musculo-ely tic media of the a rt a seen above and to the right Beneath the an urysmal sac the chordae of th tricu pid valve can be seen to the lower l ft of th picture The aortic cu p i seen in the pace between the aortic med a and the myocardium of the interventricular septum (Elastic-Van Gieson's stain X9)

Fig 6 Section from the same region of a normal heart Note the figure is laterally inverted compared with Fig 5 The bundle of His is indicated by an arrow A leaflet of the tricuspid valve is seen to the lower right and a cusp of the aortic valve to the upper left (Elastic Van Gieson's stain X9)

DR SPENCER Indeed I do

DR HEATH We ought to make the further point that these cases are now susceptible to surgical treatment I think that one of the first cases of this disease ever successfully diagnosed by cardiac catheterization and treated was in a 17 year-old girl who was operated on by Professor Allison at Leeds[1]

MR ABRAMS Surgery is almost commonplace for those cases now We have operated on a of these patients but all of them had ruptures of the right sinus of Valsalva into the right ventricle I think that rupture into the right atrium as in the present case is unusual However it would have been a nice one to sew up unless as Dr Spencer has mentioned it was in too close a proximity to the bundle of His

DR SPENCER Apparently aneurysms of the noncoronary sinus do usually rupture into the right atrium and according to Sakakibara and Konno[2] 95 per cent of the aneurysms of the sinus of Valsalva are of the right or noncoronary sinuses Ram and Menon reviewed 25 cases of congenital aneurysm of the sinus of Valsalva from the literature and found 16 cases of aneurysm of the right sinus and only 2 cases of aneurysm of the noncoronary sinus

DR EVANS Would this case be an example of Type IV in Sakakibara and Konno's classification

DR SPENCER Yes it would

DR EVANS This must be an unusually mature age for rupture to occur

DR SPENCER Well according to the same authors (Sakakibara and Konno[1b]) rupture occurs between the ages of 22 and 67 years in this particular type and they give the average age of rupture as 34 years In fact they say that the average age of rupture for all types is in the early thirties

PROF ORR Was there any evidence of dissection down the aorta?

DR SPENCER No The aortic media was normal

DR RAISON Is it not pertinent to say that the persistence of pain is perhaps the most unlikely aspect of a rupture of a sinus of Valsalva even when the onset is acute

Fig 7 The wall of the aneurysm at the site of rupture (*indicated by an arrow*) showing cardiac histiocytes (Hematoxylin and eosin X(5)

Pain for so long must surely be a remarkable feature It needs some explaining

PROF BLACKBURN I have been thinking about this and I have no explanation for these abdominal signs without heart failure which he apparently had only terminally

DR SPENCER He did have failure during the last week of life The liver showed evidence of marked fatty and congestive changes Perhaps this may account for some of the epigastric pain?

DR HEATH While we are talking about the clinical features I think that it should be made clear that the acute clinical picture in this case is only one of the ways in which ruptured sinuses of Valsalva may present When the cardioaortic fistula is not large the patient may survive for months or even years and then present at a clinic with signs of left ventricular hypertrophy a continuous murmur and a high pulse pressure In other words these patients present clinical features which are identical with those of a patent ductus arteriosus an aortopulmonary septal defect or combined aortic incompetence and stenosis Unless you refer such patients to the refinements of cardiac catheterization or angiocardiography it may be almost impossible to make a diagnosis on clinical grounds

Diagnosis Ruptured sinus of Valsalva

We wish to thank Dr I W Gallant Consultant Physician to St Chad s Hospital Birmingham for his kindness in allowing us to discuss his patient at the conference and for his cooperation in the preparation for this meeting

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Fundamentals of clinical cardiology

Management of cardiac arrest

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Cardiac arrest may be defined as *the cessation of effective cardiac output*. The word "effective" is used in the sense of maintaining a flow of oxygenated blood to vital organs of a sufficient magnitude to assure their continued viability. Under this definition it might be said that every one ultimately dies from cardiac arrest regardless of the underlying predisposing disease process.

Much of the literature on cardiac arrest in patients has been written in the past by surgeons who gained their experience mainly in the operating room. In this situation they not infrequently dealt with the arrest of a heart which was otherwise in a good physiologic and anatomic state. It is not surprising that the results of treatment in such patients should be relatively favorable. However, this is not necessarily true more recently, since surgeons now deal so often with older patients with ischemic heart disease and advanced myocardial degeneration. The internist and cardiologist, on the other hand, in the treatment of cardiac arrest are almost always exposed to problems which are quite complex. Their patients are frequently those with severe heart disease and its complications or with combinations of other significant complicating problems of cardiac and associated systemic diseases. Some of these problems involve complex disturbances in electrolyte metabolism, disturbances in acid-base balance, complex disturbances in the heartbeat, digitalis intoxication, quinidine intoxication, or other drug intoxications, cardiac tamponade, pulmonary embolization, sepsis, drug actions, autoimmunologic phenomena, acute and chronic allergic phenomena, and many others. In order to treat satisfactorily cardiac arrest under these various complex circumstances, each associated factor must be adequately evaluated and managed independently. This is frequently difficult and at times impossible. It is to be expected that the results of treatment of cardiac arrest in patients on medical wards or even in the operating room are far from satisfactory. Regardless of such poor results, the physician should be familiar with reasonably satisfactory procedures in the management of cardiac arrest. Occasionally it is rewarding.

The following discussion is oriented primarily toward the management of cardiac arrest as it might occur during the care of patients by internists and general practitioners, although these concepts may be applied by others. The presentation is to serve primarily as a simple guide to the management of this condition. Space does not permit a detailed discussion of the

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rationale for the various procedures recommended. Further information may be obtained by consulting the articles listed in the selected bibliography. The methods described here are those for external or closed chest procedures. If these procedures fail, then thoracotomy and the application of internal resuscitative measures would appear to be indicated only in highly selected situations.

Treatment of cardiac arrest

In the management of cardiac arrest which occurs in the hospital the following steps are in order.

I. Diagnosis and call for aid and supplies

A. DIAGNOSIS

1. A convulsion frequently signals the onset of cardiac arrest. Occasionally this generalized tonic contraction will last for several seconds.

2. Continued unconsciousness follows shortly after the onset of cardiac arrest, usually within 30 seconds. If unconsciousness is due to a simple faint, response should be achieved simply by placing the patient in the decubitus position.

3. Absence of respiration or the presence of gasping respiration is common. These respiratory manifestations usually follow the onset of cardiac arrest within 20 to 30 seconds. Occasionally the apneic phase of Cheyne-Stokes respiration may cause confusion, but during the apneic phase, when respiratory sounds are absent and do not cause auscultatory interference, heart sounds should be audible if cardiac contractions are present.

4. Dilatation of the pupils is an important sign. This may not become recognizable for 30 to 60 seconds after cardiac arrest.

5. There is absence of a pulse in the major arteries. Palpation of the carotid artery is probably most feasible at this point.

6. There is no audible heartbeat on auscultation of the heart.

When the diagnosis of cardiac arrest is seriously entertained, the indication for immediate institution of treatment exists. One must not wait for 100 per cent proof of the diagnosis. It is generally more dangerous to wait than to begin treatment. The length of time that circulatory arrest may be tolerated without irreversible damage to the brain depends a good deal on several factors (state of cerebral circulation, duration and degree of preceding anoxia, etc.), but in general is less than 3 to 4 minutes.

B. CALL FOR AID AND SUPPLIES. A properly trained nurse or orderly should always be on the ward of any good hospital today, trained and established to be able to institute the following procedures when notified that a patient with cardiac arrest exists.

1. Call for another physician. Ideally, two or three physicians should be summoned in order to perform effectively cardiorespiratory resuscitation.

2. Call for an anesthesiologist. An anesthesiologist can help in performing tracheal intubation and in facilitating the use of artificial ventilatory devices and oxygen.

3. Call for the cardiac arrest cart. This cart should contain the following: (a) A bedboard (in order to support the thorax if external cardiac massage is to be performed in a regular hospital bed). (b) An oropharyngeal airway (e.g., Resusitube), a bag mask apparatus, or a bellows type resuscitator. The Brook Airway has recently met with popularity. Ideally, a laryngoscope and endotracheal tube should also be available. (c) Drug tray. This tray should contain the following drugs: epinephrine, procaine amide (Pronestyl), quinidine gluconate, isoproterenol (Isuprel), atropine sulfate, one molar sodium lactate, 10 per cent calcium chloride, sodium bicarbonate, metaraminol (Aramine), levarterenol bitartrate (Levophed), parenteral adrenal steroids, 50 per cent glucose, 10 per cent calcium gluconate, regular insulin, potassium chloride for intravenous use, versenate (EDTA), angiotensin II (Hypertensin), lanatoside C (Cedilanid), and a urea solution for intravenous administration. (d) Venous cutdown tray. (e) An electrocardiograph, a defibrillator, a pacemaker, and an oscilloscopic monitor. Ideally, one should have available a direct writing electrocardiograph and a separate unit containing a combined external defibrillator, external pacemaker, and monitor.

Ideally, suction equipment and automatic cycling intermittent positive pressure breathing equipment should be available

II Sharp blow to chest This step is listed separately because of its importance and extreme value when employed at the early moment of cardiac arrest Early after the onset of cardiac arrest one need not be concerned initially about respiration since occasionally a sharp blow to the chest may restore the circulation and resuscitate the patient so that all of the more complex procedures are made unnecessary One has about 30 seconds after the onset of cardiac arrest before respirations cease The physician may give one or two sharp blows with his fist to the precordial region of the chest or he may give a few rapid strokes of external cardiac massage at the very onset The heart will frequently contract a few times or for a few seconds or minutes The physician or attendant should repeat the blows to the chest as necessary and often the heart will continue to beat spontaneously If this procedure does not meet with success one should by all means apply external cardiac massage rather than depend upon sharp blows to the precordial area

III Artificial ventilation

A OPEN AIRWAY (1) Tilt the head backward Placing a pillow under the shoulders may be helpful (2) Displace the mandible forward (3) An artificial airway if available in time is helpful and may be used but ordinarily it is not necessary Airways are useful in overcoming somewhat the esthetic objections to direct mouth to mouth resuscitation However as a patient reacts the longer pharyngeal airways may be instrumental in inducing vomiting with the danger of pulmonary aspiration Recently the so called Brook Airway has been advocated This is a short oral airway with an effective seal which is easy to use It contains a nonreturn valve which helps protect the user against communicable disease

B BREATHING The type of breathing employed will depend on the equipment available and the time at which it arrives These include (1) Mouth to mouth (2) Mouth to nose (3) Mouth to airway (4) Bag mask apparatus or bellows type resuscitator Usually an oropharyngeal airway is best employed concurrently with the use of this equipment

Once an airway is open give rapid or 4 respirations then if no help is available proceed to external cardiac massage After this give intermittent respirations (3 or 4 about every 30 seconds) When help arrives artificial ventilation is continued at a rate of about 15 to 20 per minute There is probably no real need to make an active and conscious attempt to synchronize artificial respirations with external cardiac massage so as to alternate the procedures on a fixed plan A certain rhythm usually evolves naturally

IV Artificial circulation

A FIRM SURFACE The patient should be placed on a firm surface in order to support the pressure of external massage This may be a bedboard or serving tray a stretcher or preferably the floor

B EXTERNAL CARDIAC MASSAGE Place the heel of one hand along the lower end of the sternum (above but not over the xyphoid process) of adults Place the other hand on top of the hand on the chest and compress the sternum inward 4 to 5 cm at a rate of about 60 times per minute with pressure maintained for about 0 5 second This should be done with care since the operator tends to underestimate the degree of excursions of the sternum Many complications may arise such as fractured ribs embolization of bone marrow pneumothorax ruptured liver ruptured myocardium (especially if it is freshly infarcted) or serious contusions and damage to an already diseased myocardium which may be so damaged by the massage that it will not be fit to function again

It should be noted that the obviously essential procedures listed above can be instituted by a physician or properly trained nonprofessional person working alone When help and additional supplies arrive the necessary refinements in management should be added This is the point at which the real emergency becomes less acute and a more careful evaluation and plan of management are formulated

External cardiac massage is continued until good spontaneous pulse and blood pressure are present regardless of the rhythm recorded electrocardiographically It should be recalled that in rare instances even ventricular fibrillation can be terminated by external cardiac massage and artificial ventilation alone without the

application of countershock for defibrillation.

CRITERIA BY WHICH TO EVALUATE THE EFFECTIVENESS OF THE ARTIFICIAL CARDIORESPIRATORY SUPPORT

1. Palpable pulse. The various superficial arteries should be checked periodically for pulsations produced by the external cardiac massage. These vessels include the carotid, femoral, brachial, radial, and temporal arteries. Frequently a soft tissue impulse produced by the external cardiac massage may be felt and confused with a true arterial pulse. This can occur in the carotid artery, but is especially likely in the femoral artery, particularly when the massaging hands are placed too low over the sternum and somewhat onto the epigastrium and over the abdominal aorta. It might be wise to avoid palpation of the carotid areas too firmly or entirely in certain patients. Because of the frequency of occlusive disease of the vessels of the neck and sensitive carotid sinus reflexes, cerebral blood flow might be further impeded by continued vigorous palpation.

2. Blood pressure cuff. A regular clinical blood pressure cuff may be placed on an arm and from time to time set at a pressure of 80 to 100 mm. Hg so that one may observe the deflections of the needle as external massage is carried out effectively. If this is done, the cuff should be deflated from time to time in order to avoid damage to the tissues of the limb. In observing the deflections of the needle, one should not confuse transmission of mechanical impulses with those produced by the arterial pulse.

3. Constriction of pupils and reaction to light. Careful and repeated observation of the pupils is important. Constant dilatation of the pupils and absence of response to light reflects a poor prognosis. If cardiorespiratory resuscitation is effective, the pupillary functions should be restored and preserved.

4. Return of spontaneous respiration. The absence of any indications of the return of spontaneous respiration also represents a poor prognosis.

5. Improvement in color of the skin. Cyanosis and mottling of the skin may become less intense.

6. Regaining consciousness. Certainly the return to consciousness is a favorable sign.

7. Electrocardiographic evaluation.

a. *External massage.* Massage itself produces regular wave patterns on the electrocardiogram. This mechanical stimulus may produce what appears to be electrical depolarization and repolarization. Deterioration of these waves implies a poor prognosis. In order to observe the spontaneous electrical activity of the heart, it is necessary to discontinue temporarily the external cardiac massage.

b. *Ventricular fibrillation.* The greater the amplitude of the waves of ventricular fibrillation, the better the prognosis. The more vigorous the fibrillation, the easier it is to defibrillate the ventricles.

c. *Spontaneous ventricular activity not due to ventricular fibrillation.* In general, the slower the ventricular rate, the greater the duration of each ventricular electrical complex, and the lower the amplitude of these complexes, the poorer the prognosis.

d. *With the pacemaker.* The more sharply defined the QRS-T complexes initiated by the stimulus from the electrical pacemaker, the better the prognosis. With deterioration of the QRS complexes (i.e., QRS complexes of lower magnitude, slower rate, and longer duration), the worse the prognosis. The disappearance of evidence of repolarization in the electrocardiogram carries a poor prognosis.

e. *Normal sinus rhythm.* This is obviously a good sign, but one which does not assure satisfactory or lasting cardiac output; therefore, once normal sinus rhythm has been initiated, the patient should be observed meticulously with full preparation to begin resuscitation for hours to several days. Once a patient has had a cardiac arrest, he is even more prone to develop another.

f. *Extreme sinus bradycardia.* This is frequently encountered in association with such catastrophies as a major pulmonary embolus or cerebral hemorrhage or thrombosis.

1. *Epinephrine.* Epinephrine is probably the best drug available to stimulate cardiac contractions. This drug is of help when either cardiac asystole or ventricular fibrillation is present. If asystole is present, epinephrine may convert this to ventricular

fibrillation but the final results can still be satisfactory. Epinephrine causes an increase in the vigor and magnitude of the waves of ventricular fibrillation and thus makes electrical countershock conversion easier. It should be noted, however, that epinephrine is a potent drug in predisposing to and propagating ventricular fibrillation. Therefore, overdosage should be avoided. One may wish to avoid its use or to use isoproterenol HCl (Isuprel) instead if digitalis intoxication, quinidine intoxication, or hyperkalemia is present.

If satisfactory cardiac action and clinical response have not been obtained after 1 to 3 minutes of artificial ventilation and external cardiac massage, then epinephrine may be of value. The dose of epinephrine is 3 to 5 c.c. of a 1:10,000 solution. This is obtained by the dilution of 1 c.c. of the usually available 1:1,000 solution with 9 c.c. of normal saline and the administration of 3 to 5 c.c. of this dilute solution. The 1:1,000 solution may be used directly if delay in obtaining the 1:10,000 dilution is anticipated. The route of administration generally should be intracardiac through the left fourth or fifth intercostal space preferably by using a 3½ inch No. 22 cardiac needle or spinal needle. It is important that the injection be made into a ventricular cavity and not into the myocardium itself. Injection into the myocardium may propagate ventricular fibrillation and make conversion difficult if not impossible.

If an intravenous needle is in place or an intravenous drip is running at the time and an effective circulation is being maintained by the external cardiac massage, then intravenous administration of the epinephrine with continued external cardiac massage is probably preferable to the intracardiac route in order to avoid such hazards as myocardial injection, pneumothorax, laceration of coronary artery or myocardium, hemopericardium, and the like.

Epinephrine may be repeated in the above-mentioned dose every 3 to 5 minutes as necessary, but care must be exercised to achieve but not to exceed the proper dosage.

VI. Venous cutdown and [illegible] *tracheal intubation.* Venous cutdown an[d] [illegible] of a polyethylene catheter, usually into the saphenous vein, should be performed at sometime during cardiac resuscitation. When someone trained in the procedure arrives, tracheal intubation should be considered. In general, it is usually an anesthesiologist who best performs this procedure. Tracheal intubation helps prevent the frequent complication of vomiting with pulmonary aspiration.

VII. Electrocardiographic diagnosis. An ECG diagnosis may be obtained by a direct writer electrocardiograph or by the oscilloscopic monitor. The heart may lack a spontaneous pacemaker (asystole) or have an ineffective pacemaker (ventricular fibrillation) or the heart may be unable to respond mechanically with effective ventricular contraction to one of several types of spontaneous pacemakers that might be present. Finally, the heart may lack an effective spontaneous pacemaker of its own and also be incapable of responding mechanically to an adequate degree even if an effective artificial pacemaker is applied. Therefore, in order to institute precise and proper therapy, it is of considerable value to know exactly what cardiac mechanism exists. This knowledge is afforded by the electrocardiogram and many possibilities are evident. For purposes of treatment, however, three major groups of disturbances of the heartbeat may exist.

A. VENTRICULAR FIBRILLATION. For purposes of treatment, as will be pointed out, ventricular tachycardia or ventricular flutter may also be included in this group when they are associated with signs of cardiac arrest, i.e., ineffective cardiac output.

B. ASYSTOLE. As noted later, complete heart block, a slow ventricular focus, extreme sinus bradycardia, and the so-called dying heart patterns, for purposes of treatment, may also be included in this group when associated with signs of cardiac arrest.

C. OTHER DISTURBANCES. Another group which should be considered is that in which the electrocardiogram shows fairly regular and frequent ventricular depolarization while the patient still has no effective stroke output. This disturbance frequently proceeds to asystole or ventricular fibrillation but at the moment of observation does not constitute primarily a problem [illegible]

increments The dose of 200 mg is obtained by using 2 c c from the usually available ampule which contains 10 c c with 1 Gm of the drug (100 mg per cubic centimeter) If the intracardiac route is indicated it is probably best to employ 50 mg increments of procaine amide

b *Quinidine gluconate* This is also administered slowly intravenously in increments of 200 mg This consists of 2 5 c c from the usually available 10 c c ampule which contains 0 8 Gm of the drug (80 mg per cubic centimeter)

4 Defibrillation resulting in asystole If defibrillation results in asystole then the latter is treated as outlined below Not infrequently one may observe that the period of asystole which follows countershock conversion of the ventricular fibrillation may persist for a short while or a very slow ventricular pacemaker may be present for a short while and then again revert to ventricular fibrillation (or a rapid ventricular tachycardia) The therapeutic aim during the asystolic (or slow ventricular pacemaker) phase should be to establish an appropriate pacemaker at a sufficiently fast rate as soon as possible and this in turn will help to prevent the development of ventricular fibrillation This is best accomplished by an artificial electrical pacemaker If the latter is not available then somewhat paradoxically the intravenous use of a sympathomimetic drug such as epinephrine or isoproterenol may help arouse and establish a satisfactory spontaneous pacemaker and thus retard the tendency for ventricular fibrillation to occur

B ASYSTOLE In this group in addition to complete asystole involving atria and ventricles the following states should be considered to be the same as asystole for treatment purposes complete heart block with P waves but excessively slow or absent ventricular electrical activity extreme sinus bradycardia without a faster ventricular pacemaker slow ventricular focus with or without evident P waves and the dying heart pattern

1 Avoidance of cardiac depressant drugs Such drugs as procaine amide quinidine and potassium salts are to be avoided

2 Use of electrical external cardiac pacemaker This is probably the best means of initial treatment of cardiac asystole If after several shocks no clinical improvement is noted and no arterial pulse is detectable then stimulation is stopped external massage is resumed and attempts to augment the myocardial response by drugs are employed as needed One may augment the myocardial contractile or mechanical response to electrical stimulation when it is insufficient by using epinephrine isoproterenol (Isuprel) one molar sodium lactate or calcium chloride in dosages outlined below

Details of operation of the external cardiac pacemaker vary somewhat with the various models available Obviously it is wise to be familiar with the operation of the particular apparatus to be used before an actual emergency arises In general in the unconscious patient it is well initially to use the higher voltages available This may be reduced to threshold levels after a satisfactory response is obtained The heart should be paced at a rate of 60 to 70 per minute Remember that a satisfactory result can be obtained only when the myocardium is capable of an effective contractile or mechanical response to the electrical stimulus Furthermore the pacemaker is ineffective in the presence of ventricular tachycardia or ventricular fibrillation

The stimulus from the external pacemaker in addition to producing the desired effect of myocardial stimulation also produces significant contractions of the skeletal muscles over the chest wall In the unconscious patient this is not a problem but in the conscious patient analgesics and sedatives are required to control the discomfort produced Voltages approaching threshold levels are desirable In general with well lubricated (electrocardiographic jelly) and properly placed electrodes ventricular contractions can be produced with about 70 volts in a patient of average size

The presence of an electrical myocardial response to the external pacemaker stimulus as manifested by T waves on the electrocardiogram although representing a favorable sign cannot be relied upon as evidence that effective ventricular contractions are being produced There must be a good mechanical response indi

by palpable peripheral pulses and general improvement in the clinical state of the patient It should be recalled that the amplitude of the T wave varies with the electrocardiographic lead employed so that more than one lead should be recorded before the conclusion is drawn that an adequate electrical response has not been achieved

Unfortunately only a few patients with cardiac asystole respond to the cardiac pacemaker unless the asystole is due primarily to disease of the conducting tissues (in particular atrioventricular heart block) or to drug toxicity (digitalis quinidine procaine amide) Nevertheless when available the pacemaker is the best initial means of treatment after emergency external cardiac massage

3 Resort to drugs If a cardiac pacemaker is not available then asystole is treated by means of drugs with continued external cardiac massage The following drugs are of value in initiating and supporting spontaneous electrical activity of the heart and in effective contractile response to this stimulus

a *Epinephrine* The dose is 3 to 5 c c of a 1 10 000 solution given intravenously or by the intracardiac route as outlined earlier in this presentation This may be repeated every 3 to 5 minutes as necessary After a spontaneous pacemaker is initiated it may be supported by 0 2 to 0 5 c c of 1 1 000 epinephrine subcutaneously or intramuscularly repeated every 30 to 60 minutes as necessary or by epinephrine in oil 0 5 to 1 0 c c intramuscularly every 6 to 12 hours repeated as necessary Not infrequently however one finds that the drug appears to be effective in maintaining a satisfactory pacemaker only by the intravenous route To avoid repeated intermittent injections one may wish to administer epinephrine by intravenous drip In this situation 4 mg of epinephrine (4 c c of 1 1 000 solution) may be diluted in 1 000 c c of fluid and given at a rate of 15 to 30 drops (4 to 8 μg) per minute An increase or decrease in the rate of infusion is then made according to the response observed

b *Isoproterenol* (*Isuprel*) The intravenous or intracardiac dose of this drug is 0 02 to 0 04 mg This is prepared by diluting the usually available 1-c c ampule (which contains 0 2 mg) up to 10 c c and administering 1 or 2 c c of this dilute preparation This may be repeated every 3 to 5 minutes as necessary As outlined for epinephrine isoproterenol may also be administered by intravenous drip using 1 or 2 mg (5 to 10 c c) diluted to 200 to 500 c c with isotonic saline or glucose solution and administered over 2 to 3 hours or as required to achieve the appropriate response Isoproterenol may be also given by the intramuscular or subcutaneous route in a dose of 0 2 mg (1 c c) and repeated every 1 to 6 hours as necessary The dose route and rate of administration will depend obviously on whether one is trying to initiate spontaneous cardiac activity or simply to support a suitable mechanism already developed

The following points may be of help in deciding whether to use epinephrine or isoproterenol in the treatment of cardiac asystole Epinephrine would appear to be preferable if there has been no detectable ventricular fibrillation preceding the asystole Isoproterenol would appear to be preferable if there has been preceding ventricular fibrillation especially if the fibrillation waves have been vigorous and of good amplitude Epinephrine is a potent agent in stimulating the myocardium and in predisposing to the development of ventricular fibrillation In contrast isoproterenol has less of a tendency to do this since it seems to produce a more selective stimulation of the higher (sinoatrial node atrioventricular node etc) rather than the lower (myocardium) cardiac pacemaker centers It should be recalled that isoproterenol may cause a significant degree of peripheral vasodilatation with resulting hypotension in certain patients Because of this vasopressors may need to be added in these instances Contrariwise epinephrine may cause a considerable rise in blood pressure in certain patients The desired blood pressure response may thus be an important factor in deciding which drug to use at a given time

c *One molar sodium lactate* The intracardiac dose is 10 to 20 c c The intravenous dose is 20 to 80 c c over a period of 1 minute up to 1 liter administered in 5 hours This drug seems to be much less able than

epinephrine or isoproterenol to initiate an effective cardiac pacemaker However it may effectively maintain or accelerate a pacemaker once it has developed

d *Atropine sulfate* In some patients with high degree or complete heart block the parenteral administration of atropine may have a very beneficial effect especially through promotion and stabilization of atrioventricular conduction This is particularly so in patients with recent onset of heart block associated with acute myocardial infarction (usually a posterior infarction with occlusion of the right coronary artery) in whom a favorable effect may be dramatic The dose of atropine varies from 0 4 mg (grain 1/150) intramuscularly to 1 mg (grain 1/60) or even 2 mg (grain 1/30) intravenously The drug may be repeated every 2 to 6 hours as needed

In the management of complete heart block with an unsatisfactory spontaneous pacemaker the procedures alluded to above are primarily for the acute emergency period Later a cardiac catheter with an endocardial electrode may be passed into the right ventricle and an external electrical stimulus applied as a pacemaker This is usually a temporary procedure For long term management an implantable direct internal cardiac pacemaker is inserted This has proved to be highly satisfactory A discussion of the latter two means of management is beyond the scope of this presentation but the indications methods and results of such procedures should be familiar to physicians responsible for these patients

IX Other drugs

A CALCIUM CHLORIDE If epinephrine is ineffective or if contractions are weak as indicated by the complexes of the electrocardiogram and the lack of an arterial pulse then calcium chloride may be given The dose is 3 to 10 c c of a 10 per cent aqueous solution of $CaCl_2$ administered slowly by the intravenous or intracardiac route This may be repeated every 3 to 5 minutes as necessary with care being taken not to administer too much Calcium chloride should probably be avoided if digitalis toxicity is suspected

B SODIUM BICARBONATE When the circulation is arrested (i e there is no spontaneous cardiorespiratory activity) for 5 minutes or more severe acidosis results Sodium bicarbonate should be administered It is generally available in 50-c c ampules which contain 3 75 Gm (44 mEq) of sodium bicarbonate The dose is 1 ampule administered slowly by the intravenous route The drug should be repeated about every 10 minutes up to a total of 6 to 7 ampules as long as circulatory arrest continues One must continue to ventilate the patient well after $NaHCO_3$ is given in order to help eliminate the carbon dioxide which is released

C VASOPRESSOR DRUGS Vasopressor drugs are frequently indicated to maintain the blood pressure at suitable levels during the immediate period of follow up management of the patient with cardiac arrest In this situation it is probably best to administer one of the cardiotonic type of vasopressor agents

1 Metaraminol (Aramine) One hundred to 400 mg of metaraminol should be diluted in 500 c c of normal saline or 5 per cent dextrose solution and given by intravenous drip at a rate sufficient to control the blood pressure at a satisfactory level This drug is supplied in 10-c c ampules with each cubic centimeter containing 10 mg

2 Levarterenol bitartrate (Levophed) Four to 5 ampules (0 2 per cent solution with 4 c c per ampule) of levarterenol bitartrate should be diluted in 500 c c of normal saline or 5 per cent dextrose solution and administered by intravenous drip One ampule (5 mg) of phentolamine (Regitine) may be added to this solution in order to help prevent necrosis should the fluid extravasate into the surrounding tissues One should attempt to maintain the blood pressure at a level of about 100 mm Hg systolic depending of course on the level of arterial blood pressure prior to the arrest and on whether the kidneys are producing urine at the proper rate (over 0 5 c c per minute is acceptable)

D ADRENOCORTICAL STEROIDS In certain situations the administration of one of the adrenal steroids might be of value Hydrocortisone (Solu Cortef) can be administered in a dose of 100 mg intravenously Other drugs that may be given are prednisolone (Hydeltrasol) in a dose of 20 to

mg. intravenously or intramuscularly, or methylprednisolone (Solu-Medrol) in a dose of 20 to 50 mg. intravenously or intramuscularly.

V. *Special situations.* The following situations are encountered during the treatment of cardiac arrest on a medical ward.

A. GASTRIC DILATATION. This may be one of the underlying causes of the cardiovascular collapse. It may have been aggravated or caused by the artificial ventilation. It is treated by passage of a gastric tube with aspiration of the gastric contents and careful lavage with $NaHCO_3$.

B. HYPERKALEMIA. This might occur if renal failure is present or if potassium has been given injudiciously. In the emergency situation it is best treated by the fairly rapid intravenous administration of a solution which contains 350 c.c. of 50 per cent glucose, 2 ampules (40 c.c. per ampule) of one molar sodium lactate, 2 ampules (10 c.c. per ampule) of 10 per cent calcium gluconate, and 50 units of regular insulin.

C. DIGITALIS INTOXICATION. Potassium, versenate (EDTA), or antazoline, depending upon the type and degree of digitalis intoxication present, may be used separately or in combination for digitalis intoxication.

D. QUINIDINE INTOXICATION. Molar sodium lactate, isoproterenol, levarterenol, angiotensin II (Hypertensin), and versenate may be used for quinidine toxicity, depending upon the amount of quinidine that has been given, the duration of toxicity, and the severity of the symptoms.

A discussion of the details of management of hyperkalemia or of digitalis or quinidine intoxication is beyond the scope of this presentation. However, the physician should be familiar with these details in order to manage properly many instances of cardiac arrest. It might be noted that cardiac asystole attending intoxication with these drugs usually responds relatively well to the external cardiac pacemaker, depending of course upon the presence of an otherwise good myocardium.

E. PULMONARY EMBOLISM. The following drugs may be of value in the emergency treatment of pulmonary embolism: (1) atropine sulfate given in a dose of 1 mg. (1/60 grain) intravenously, (2) isoproterenol by intravenous drip as outlined above. Other means employed in the treatment of pulmonary embolism are beyond the scope of this presentation.

VI. *The postresuscitation treatment.*

A. ELECTROCARDIOGRAPHIC MONITORING. Constant observation by a capable attendant with continuous or frequently repeated electrocardiographic monitoring is extremely valuable. One should be prepared to reinstitute immediately external defibrillation or pacemaking as the need arises. Recurrence of a previous disorder of mechanism is common and carries a poor prognosis.

B. VITAL SIGNS. The continuous or frequently repeated observation and recording of vital signs are important.

C. CONTINUED VENTILATORY ASSISTANCE. Frequently, after conversion to a satisfactory mechanism, spontaneous respirations are still inadequate; therefore, continued ventilation is indicated, preferably employing 100 per cent oxygen. One of the automatic cycling devices such as the intermittent positive pressure machines may be used. At this time a tracheotomy might be performed and a tracheal attachment for the intermittent positive pressure machine utilized.

D. INDWELLING BLADDER CATHETER. To facilitate checking the urinary output, an indwelling bladder catheter may be necessary. The volume of urinary output is important in judging the adequacy of the blood pressure and the circulation. The rate of urinary excretion should preferably exceed 0.5 c.c. per minute.

E. VASOPRESSORS. Blood pressure support with vasopressor drugs, as outlined previously, may need to be continued.

F. DIGITALIS. The decision of when digitalis should be administered is occasionally difficult to make. Recently there has been a trend to the more liberal use of digitalis even if classic indications are not obvious.

G. ANTIBIOTICS. Gram-negative bacteremia is common after prolonged shock. Culturing of blood and the appropriate use of antibiotics are frequently indicated.

H. HYPOTHERMIA. If the patient awakens after the resuscitative measures, hypothermia, which is used to decrease the formation of cerebral edema, is not indicated. If the patient does not awaken after

the resuscitative procedure and the establishment of good cardiac output then ideally hypothermia should be instituted immediately One may use either the refrigerated blanket or the ice mattress or the patient may be packed in ice The rectal temperature should be lowered to 32 34° C (89 93 F) and maintained there for 48 to 72 hours or until evidence of brain damage disappears The best method for controlling the shivering which is present during the use of hypothermia appears to be the use of succinylcholine

I UREA Urea is used in an attempt to lessen the cerebral edema Forty to 120 Gm of a solution of urea is administered intravenously over a period of 30 minutes to 2 hours immediately after the completion of the resuscitative procedures This is then repeated in approximately 6 hours as necessary One may use Urevert which is supplied in kits containing 40 Gm of lyophilized urea and which when reconstituted provides 120 c c

J HYPERVENTILATION AND BODY POSITION Cerebral edema may be further prevented by hyperventilation through the automatic cycling device and by elevation of the head of the bed

K FINDINGS INDICATIVE OF IRREVERSIBLE DAMAGE These include (1) persistent dilatation of the pupils (2) unconsciousness lasting for 1 to 2 hours or more (3) no spontaneous respirations after 1 hour (4) no spontaneous cardiac electrical activity after 1 hour and (5) segmentation (box-car effect) of the blood in the retinal vessels

General remarks

Cardiac resuscitation by opening the chest surgically with direct cardiac massage is not only frequently ineffective but usually contraindicated in patients with serious ischemic heart disease These people with stand poorly or not at all the severe trauma of a thoracotomy It is amazing how impulsively a physician will open a patient s chest for direct cardiac massage and resuscitation in the presence of advanced ischemic heart disease but will deliberate for hours over the advisability of a relatively minor surgical procedure in the same patient or another because of ischemic heart disease Patients with adv coronary artery disease do not withstand thoracotomy readily and do not respond satisfactorily to resuscitation Failures are extremely common in them even when external resuscitative procedures are used The external method is the one of choice and it should be mastered in detail

Certainly the procedure of open-chest and direct cardiac massage should not be employed unless necessary drugs and surgical and other adequate apparatus and equipment are available for if resuscitation is achieved and especially if the patient regains consciousness one can readily appreciate the dramatic confusing situation that the patient and physician will experience It is likely that if the patient can be satisfactorily resuscitated properly applied external methods will be effective Obviously it is much better that a patient regain consciousness with a closed intact chest Furthermore when he recovers there is not the painful and debilitating surgical procedure of open-chest resuscitation to impair or inhibit his continued return to complete recovery Open thoracotomy is a serious situation itself and should not be imposed upon an already seriously sick person unless unavoidable

The physician must remember that once the immediate phase of cardiac resuscitation has been achieved the patient must be carefully and constantly watched in anticipation at all times of another episode of arrest Such patients should not be left alone for some while When the patient s health permits the cause for the arrest should be determined and properly treated Once the arrested heart has been started again the physician s responsibilities are not over

It is likely that separate intensive care units with central monitoring equipment will be employed with increasing frequency in hospitals in the near future This will obviously allow closer observation of patients in whom the risk of cardiac arrest is high such as those with acute manifestations of coronary artery disease or those who have already suffered one episode of cardiac arrest Proper staffing with specially trained personnel will promote earlier detection and institution of appropriate treatment of cardiac arrest and should result in an improvement of the prese

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taps and to suggest that much further detailed morphologic and physiologic study is required to assign a proper place to these structures Their significance in clinical situations is not considered here but they must play an important role

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Dialysis for chronic renal failure

Artificial dialysis was reported a few years ago by John Merrill to produce beneficial effects which persisted for some months in an occasional individual with chronic renal failure Paul Teschan in the Renal Center at Brooks Army Hospital dialyzed patients with chronic renal failure at biweekly intervals but in so far as I can determine he has not reported on his experiences In order to enable a patient with irreversible renal failure to maintain a reasonable state of activity it is necessary to perform dialysis about every 2 weeks for a period of [illegible] hours The disadvantages of the old techniques employing the Kolff rotating drum or even the Kolff twin-coil dialyzer were (1) the need for two or more units of blood to prime the machine (2) the necessity of cutting down on the artery and vein each time and (3) the requirement of skilled professional personnel for long periods of dialysis Belding Scribner surmounted one of these obstacles with a cannula which provides a continuous flow of blood from artery to vein when the arterial and venous parts of the cannula are fitted into one another The may then be separated as often as desired and attached to a dialyzing machine He also employed a pumpless low temperature hemodialysis system which requires relatively less attention than the earlier model In addition to these he gave repeated peritoneal dialysis utilizing a semipermanent button modified from one originally described by Merrill He found that patients developed peripheral neuritis and had severe malaise unless they received treatment twice a week At first patients under 40 years of age who were emotionally stable were used but soon the demand became so great that a Citizens Committee was set up to weigh the relative value of each candidate to the community in order to decide who should receive treatment

Recently Barry and his group[a] have devised a self retaining cannula with a balloon which can be used for repeated dialysis

Since then Harold McDonald John Weller and collaborators at the University of Michigan have experimented with a self-dialysis type of therapy in which the patient performs his own peritoneal dialysis A similar study is going on in Merrill s group at the Peter Bent Brigham Hospital Much supervision is required and peritonitis has occurred more than once in several patients but has been quite easily controlled by antibiotics

oscilloscope A small blip artefact results from such a discharge if one of the electrode paddle wires is wound several times around the left or right arm electrocardiograph lead wires With newer auto synchronizing instruments the procedure is simplified for the discharge can only be released during inscription of the QRS This can be readily recognized as a brief isoelectric line distorting the terminal portion of the QRS complex

Once the accuracy of the synchronizer is established the patient is given about 100 to 150 mg of sodium thiopental intravenously The objective is to induce neither anesthesia nor unconsciousness but rather transient amnesia Muscle relaxants are not necessary The two electrode paddles are coated with a thick layer of conductive paste and applied with firm pressure on the chest wall Early in our experience one electrode was placed over the right parasternal area of the third intercostal space and the second electrode in the left mid axillary line at the level of the fifth intercostal space A better placement of the electrodes is achieved by shifting the electrode from the mid axillary position to the left infrascapular area This shortens the pathway between electrodes and augments the density of the electrical field which traverses the heart thereby diminishing the energy required for reversion (see Table I) Animal studies indicate that there is no danger of injuring the spinal cord

The initial energy setting is 50 w s If the arrhythmia is not reverted the next discharge is at 100 w s and thereafter the energy is increased by increments of 100 w s until a discharge of 400 w s has been given If it is clear that fibrillation is continuing successive discharges can be given without delay If however no atrial activity is evident it may be necessary to take a brief strip of Lead V_1 to ascertain the underlying mechanism Absence of f waves and slowing of the ventricular rate indicate the presence of nodal rhythm Such a transitional mechanism is observed in a number of patients before resumption of sinus rhythm Further shocks are therefore to be avoided If normal rhythm persists for only 1 or 2 minutes it is worth while to repeat the procedure because some patients will

*Table I Comparison of distribution of energies required for reverting 133 episodes of atrial fibrillation with two paddle placement**

Electrode placement	Energy required (watt seconds)			Total episodes
	≤100	200	≥300	
Anterolateral	33	15	15	63
Anteroposterior	60	8	2	70

*Patients reverted with permanent ... after mitral valve surgery ... were excluded
$X^2 = 19.5$
$p < .001$

maintain a sinus rhythm thereafter If however sinus rhythm is transient after a second reversion the antiarrhythmic drug program is inadequate and further cardioversion attempts should be abandoned until this can be remedied

The entire procedure requires about 30 minutes The patient s response to the electrical discharge consists of a single twitch of thoracic muscles a slight jerk of the arms and at times an audible sigh The patient is usually awake within 2 to 5 minutes and is released from the recovery room within an hour All patients are continued on quinidine maintenance therapy

Recently the need for anesthesia has been questioned[8] Patients cardioverted without anesthesia are premedicated with intramuscular meperidine (0 1 Gm) and secobarbital (0 1 Gm) Pain is not experienced The sensation is that of a sudden jolt or a transiently felt pressure across the chest The degree of discomfort varies directly with the energy discharge Our experience indicates that when the energy setting is 100 w s or less cardioversion without anesthesia is well tolerated Until criteria emerge for predicting energy requirements for reverting the individual patient transient amnesia induced by thiopental will remain the procedure of choice It is our practice to dispense with anesthesia in some patients with thin chests in those with atrial fibrillation of recent onset and in patients whose approximate energy requirement has been established as being 100 w s or less during previous reversions The anteroposterior electrode placement by reducing energy requirements facilitates reversion without anesthesia

A question as yet unanswered is whether anticoagulant drugs should be employed routinely for patients undergoing cardioversion No ready answer is available from the much larger experience with quinidine-induced reversion of atrial fibrillation The magnitude of the risk of embolism caused by restoring atrial contraction remains uncertain Our practice has been to use anticoagulants for patients who have recurrent systemic emboli and for those well compensated patients with mitral stenosis who have atrial fibrillation of recent onset When anticoagulants are employed they are administered for 3 weeks before and 1 week after the cardioversion

The immediacy of results the simplicity of this method the high yield of successful reversions and the relative infrequency of complications recommend cardioversion as the treatment of choice for restoring sinus rhythm in patients with chronic atrial fibrillation

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developed before the child is 24 to 30 months of age[13] Lower limb prostheses are fitted as soon as the child shows a desire to stand When both lower limbs are represented by vestigial remnants a bucket type of device is made into which the child is fitted and this may be mounted on wheels for locomotion Surgical procedures may be required but every effort should be made to preserve as much tissue as possible A vast amount of research is being carried out to provide some external source of power to drive the prostheses used when all four limbs are rudimentary or ab nt

These children suffer more from heat than cold and have a tendency to sweat excessively The pediatrician has an important task in advising on everyday management in regard to both the physical and emotional development of the child The therapists must guide and instruct from the early stages in order that normal patterns of movement may be developed. Prosthetic management is difficult[12] but there is a wide variety of devices to provide assistance and research is proceeding in many centers *Assessment by a psychiatrist and psychologist* is desirable. Depression and self-castigation have been reactions noted in some parents Parents must be fully informed of the prognosis for the future development of the child In the early years the social service worker[10] plays a supporting role later the *problems are those of education* Eventually the handicapped child must assume the responsibilities of an adult The aim is to achieve maximal independence both in daily living and hopefully in an occupation

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Editorial

The advantages of research on man

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Regardless of the species of animal they study, the physiologist and biochemist frequently extend the interpretation of their data to apply to man. The contributions toward a better understanding of human biologic function obtained by experimentation on animals other than man is well recognized. The difficulty of translating physiologic responses in one species to other species has been discussed many times and needs no further emphasis. However, besides the obvious fact that to learn human responses it is best to study man, there are other advantages to research on human beings. Perhaps these advantages are well known only to those who have studied man himself. Because man may be awake and responsive throughout a study, he can participate, if necessary, in the study or at least report his experiences during the experiment. Furthermore, the investigator need not be concerned about the influence of an anesthetic agent. In turn, the investigator must be deliberate and exact in his experimentation. The conscious human subject provides a continuous stimulus to the investigator to be accurate and careful, and this cannot help but be reflected in the data which he obtains. This is not to say that studies on animals other than man are carelessly executed. However, they may be. Laboratory animals are readily available, whereas man is not. Investigators who study man must have a degree of confidence and responsibility which is required of no other type of investigator.

There is a greater tendency to salvage an experiment when working with laboratory animals than when working with man. If an expected response to a particular drug does not occur, larger and larger doses of the drug are often given until something resembling the expected response occurs. Although there is nothing wrong with this approach, the results must be scrupulously analyzed and reported. When working with man, there is little tendency to administer excessive dosages of a drug. Not only are the dosages of drugs kept relatively constant from subject to subject, but negative results are accepted as such, and no effort is made to obtain a response with large and physiologically unsound dosages of the experimental drug.

Those who work with laboratory animals frequently have no knowledge of the state of health of the experimental animal prior to the study. On the other hand, before

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Clinical communications

Systemic amyloidosis presenting as constrictive pericarditis A case studied with cardiac catheterization

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Primary systemic amyloidosis is a rare disorder that has been diagnosed *pre mortem* with difficulty Yet in 51 fatal cases presented by Lindsay[1] death was attributable in 22 to cardiac failure and in 18 of these the amyloid involvement of the heart was responsible for this failure Recently it has been pointed out that systemic amyloidosis can present a clinical picture similar to that of constrictive pericarditis [7] It appears that in some of the patients who present in congestive heart failure a diagnosis might be made *ante mortem* if this clinical similarity were remembered

The following is the report of a case of primary systemic amyloidosis presenting as constrictive pericarditis and studied with the aid of right heart catheterization

Case report

E H M (UMH #934019) was a 49 year old truck farmer who in late February 1959 passed a life insurance examination demonstrating good exercise tolerance and a normal urinalysis In May he developed rapidly progressive exertional dyspnea which caused his hospitalization elsewhere with hepatomegaly In June he lost his taste for cigarettes and noted increasing abdominal distention swelling of the ankles and trepopnea without orthopnea Because of unresponsiveness to digitalis and diuretics he was admitted to the University of Michigan Hospital on Aug 22 1959

On physical examination he was slightly icteric and lay flat in bed without discomfort despite anasarca His blood pressure was 90/70 mm Hg with a paradoxical pulse which measured 8 mm The pulse rate was 92 and the respiratory rate was 14 per minute There was marked distention of the neck veins even when he was in the sitting position and evidence of bilateral pleural effusions No rales were heard The heart was enlarged to the left anterior axillary line and the point of maximum impulse was absent The heart sounds were of good quality with an accentuated P and a *protodiastolic* extrasound along the left sternal border No murmurs were heard The abdomen was markedly distended by ascites and a hard liver which was enlarged to just below the iliac crest and umbilicus There was 4+ edema of the scrotum thighs and ankles The remainder of the examination was unremarkable

The hemoglobin was 16 ? Gm per 100 ml with a hematocrit of 53 per cent the erythrocyte sedimentation rate was 2 mm per hour the white blood cell count was 8 900 per cubic millimeter with 77 mature polymorphonuclear leukocytes 1 band form 12 small lymphocytes and 10 monocytes per hundred The urinalysis was normal except for an initial 4+ protein which subsequently fell to trace There was no Bence Jones protein The blood urea nitrogen was 37 mg per 100 ml the alkaline phosphatase was 33 5 KA units and total bilirubin was 3 6 with 1 minute direct of 1 6 mg per 100 ml Thymol turbidity cephalin cholesterol flocculation and prothrombin concentration were normal The total serum protein were 6 5 Gm per 100 ml with an A/G ratio of 3 3 and an electrophoretic pattern that showed a slight increase in alphas and beta globulins

Cardiac fluoroscopy demonstrated cardiomegaly and decreased amplitude of pulsations An electrocardiogram showed small QRS complexes and flat

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Discussion

This case presented several interesting points to the clinician. The first was the establishment of the diagnosis of amyloidosis. It was believed that severe failure of the right side of the heart might be a feature of a disease with multisystem involvement. The presence of plasmacytosis (or multiple myeloma) suggested either amyloidosis or paramyloidosis. This was confirmed by gum biopsy.

Differentiation between multiple myeloma with paramyloidosis and amyloidosis with plasmacytosis is difficult, but the latter diagnosis was favored because of the benign appearance of the plasma cells.

A third and thought-provoking facet was the resistance of the failing amyloid heart to intensive therapy.

The last interesting feature of this case is its similarity to constrictive pericarditis. In pericarditis the fibrosing process involves both the right and left sides of the heart and quite reasonably restricts the usual ventricular distensibility. This restriction is reflected in a rather characteristic pressure pulse tracing on right heart catheterization first described by Bloomfield and associates[9] and subsequently studied and further defined by others.[10-12] Briefly, the changes include an early diastolic dip in the ventricular pressure which does not fall to normal values and a rapid rise to a sustained elevated end-diastolic plateau. The subsequent systolic peak pressure is often elevated. However, the ratio of the pressure of the diastolic plateau to the ventricular systolic peak is characteristically greater than 0.3. The diastolic right atrial pressures generally reflect the changes which are occurring in the right ventricle and thus demonstrate an increased mean pressure and a series of dips which give the tracing an M or W appearance.

That pericardial calcification alone and even the fully developed clinical picture of constrictive pericarditis need not be associated with the characteristic right-sided pressure pulse tracings was pointed out by Harvey and associates[14] and Lin and Anache[8] respectively. On the other hand, it has been shown that several other pathologic entities can give a picture quite similar to that of constrictive pericarditis both clinically and on catheterization of the right side of the heart. In 1946, Bloomfield and associates[9] noted that severe right-sided heart failure could produce similar tracings. This finding was substantiated by Wilson and associates,[11] who added acute pericardial effusion to the growing list. Myocardial fibrosis due to coronary atherosclerosis,[15] nonspecific myocarditis,[16] subendocardial fibrosis,[17] and cardiac hemochromatosis,[18] as well as limitation of ventricular distensibility due to *pectus excavatum*[19] have all been reported to produce right-sided pressure pulse tracings identical to those of classic constrictive pericarditis. Balchum and associates[18] went even further and suggested several entities that reasonably could be expected to give similar tracings. Among these are myocardial fibrosis associated with scleroderma heart disease and certain neurological entities, glycogen storage disease, and fatty or neoplastic infiltration. It is apparent, therefore, that the pressure pulse tracings obtained in constrictive pericarditis are not pathognomonic.

This lack of specificity seems to be quite logical when one considers amyloidosis in more detail. The extensive diffuse or nodular interstitial deposition of amyloid in the myocardium, as well as the infiltration of the endocardium and pericardium by this rather rigid material,[6] cannot but cause a decrease in the normal excursions of the ventricular chambers. The result[3] is an abnormal physiology similar to that described by Lyons and Burwell[1] for constrictive pericarditis. Specifically, right heart catheterization studies in this patient demonstrate changes in pressure which are identical to those described in chronic constrictive pericarditis. The same is true for the three previously reported cases of amyloidosis with cardiac involvement that have been studied with right heart catheterization.[4-7] In cardiac amyloidosis, as the right ventricle enters early diastole, the blood rushes under an increased pressure into the inelastic ventricular chamber. Because the ventricle is unable to dilate sufficiently, the pressure in this chamber never falls to less than 5 mm. Hg (Fig. 1) and instead again rises rapidly until the pressures in the two chambers and the

venous system are equalized at an elevated sustained end diastolic plateau The result is the early diastolic dip and plateau seen also in the tracings from patients with constrictive pericarditis These changes in diastolic pressure are reflected in the atrial pressure tracings (Fig 2) On auscultation this sudden change in pressures produces the protodiastolic extra sound noted also in this patient On the other hand the right ventricular pressure in the normal person remains below 5 mm Hg throughout this period because the ventricle is able to dilate (Fig 3) During ventricular systole the peak pressure reaches 48 mm Hg and is a reflection of pulmonary hypertension In this case it is possibly due not only to inflow stasis on the left side of the heart because of amyloid restriction but also to amyloid deposition in the pulmonary arterioles Although Yu and associates[1] have considered a ratio of the end-diastolic to peak right ventricular pressure greater than 0 3 to be diagnostic of constrictive pericarditis in this patient it was 0 52

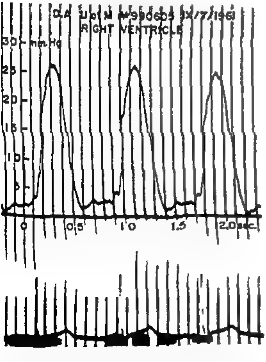

Fig 3 A normal person s right ventricular pressure tracing (*upper curve*) and Lead II of his electrocardiogram (*lower curve*) Note the difference in the pressure scale

It is clear therefore that the reported changes in right ventricular pressure in amyloidosis with cardiac involvement are indistinguishable from those seen in chronic constrictive pericarditis Amyloidosis must then be considered in the differential diagnosis in patients who present with a clinical picture of constrictive pericarditis

Summary

A case of systemic amyloidosis and plasmacytosis is presented Both on clinical observation and cardiac catheterization the features of this case simulated those of constrictive pericarditis The pertinent literature is reviewed

I wish to thank Dr C W Castor Jr of the Arthritis Unit and Dr W S Wilson of the Heart Station for reading the manuscript for their encouragement and for their many helpful criticism

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Table II

Patient number	Cardiac index (liters)	Stroke index (ml)	Oxygen consumption (ml / M²)	Arteriovenous oxygen difference (vol %)	% Oxygen coefficient	Systemic vascular resistance (units)	Pulmonary vascular resistance (units)	Right ventricular work (Kg /min / M²)	Left ventricular work (Kg /min / M²)
Before Operation									
9	4 35	43 5	163	3 8	28 7	15 3	1 36	0 64	4 89
10	4 3	65 1	176	3	25	13 3	2 1	1 35	5 33
11	4 5	59 1	157	3 5	26 3	12 1	0 83	0 71	6 01
12	3 17	44 5	134	4 5	26 8	15 3	0 55	0 26	3 86
13	3 9	46 7	204	3 4	23 9	10 9	0 [illegible]	0 6	4 47
14	4 83	67 1	176	4 7	35 9	11 1	2 26	1 38	5 77
15	3 49	46 1	118	5	30 1	15 9	2 6	1 1	4 33
16	3 27	39 3	165	3 6	28	17 6	1 93	0 68	4 06
17	4 9	59 4	175	3 4	24 4	9 4	0 57	1 19	5 14
18	3 97	61 2	—	3 3	27 3	14 7	1 8	1 13	5 29
Avg	4 068	53 24	163 1	3 82	27 64	13 56	1 47	0 904	4 915
After Operation									
19	4 9	56	195	2 4	23	9 5	1 26	0 98	5 62
20	3 66	41	158	4 3	25 5	11 9	0 74	0 309	4 2
21	3 1	31 1	118	3 7	[illegible] 6	22 1	2 73	0 702	4 71
22	8 2	92 9	120	1 5	11 2	4 8	0 3	1 81	8 62
23	6 2	80	177	2 6	26 1	7	0 21	0 78	8 004
24	5 4	54 2	165	2 9	19 9	11 4	0 53	0 62	5 44
25	9 6[illegible]	96 2	183	1 9	14	6	0 48	2 07	10 57
26	4 77	63 5	156	3 2	22	8 7	0 78	0 9	4 79
Avg	6 25	60 47	165	2 68	20 24	8 41	0 614	1 067	6 747
S E D	0 526	7 7	12 075	0 384	7 4	1 3	0 313	0 244	0 76

Portocaval shunt operation and splenectomy
Avg Average S E D Standard error of deviation

(S E 0 526) which is also significant at the 5 per cent level (t +4) The increase in cardiac output was mainly the result of an augmented stroke volume rather than an increased heart rate

STROKE INDEX Before operation the average stroke index for the 18 patients studied was 55 ml For the 8 patients with paired observations it was 55 9 ml and became 72 ml after the operation with an average increase of 16 1 ml (S E 4 482) which is significant at the 5 per cent level (t +3 55)

In the group of patients with unpaired observations the average before operation was 53 24 ml and that after it was 60 47 ml with an increase of 20 32 ml (S E 7 7) which is also significant at the 5 per cent level (t +2 64)

OXYGEN CONSUMPTION (Fig 2) Before operation the average oxygen consumption for the 18 patients studied was 167 9 ml /M For the 8 patients with paired observations it averaged 172 5 ml /M² and it became 176 1 ml /M² after operation with an increase of 3 6 ml (S E 8 006) which is insignificant at the 5 per cent level (t +0 447)

In the group of patients with unpaired observations the average before operation was 163 1 ml and that after it was 164 8 ml with an increase of 1 7 ml (S E

12 075) which is also insignificant at the 5 per cent level (t +0 103)

ARTERIOVENOUS OXYGEN DIFFERENCE (Fig 3) Before operation the average arterio venous oxygen difference for the 18 patients studied was 3 7 vols per cent For the 8 patients with paired observations it averaged 3 6 vols per cent before operation and it became 2 4 vols per cent after the operation with a decrease of 1 2 vols per cent (S E 0 289) which is significant at the 5 per cent level (t −4 2)

In the group of patients with unpaired observations the average before operation was 3 82 vols per cent and that after it was 2 68 vols per cent with a decrease of 1 14 vols per cent (S E 0 384) which is also significant at the 5 per cent level (t −2 919)

SYSTEMIC VASCULAR RESISTANCE (SVR) (Fig 4) Before operation the average SVR for the 18 patients studied was 12 9 units (1 032 dynes sec cm ⁵) For the 8 patients

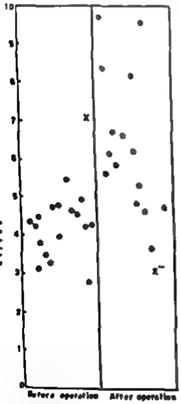

Fig 1 Cardiac index before and after operation X Patient 5 X̄ Patient 21 underwent splenectomy 2 years before the shunt operation

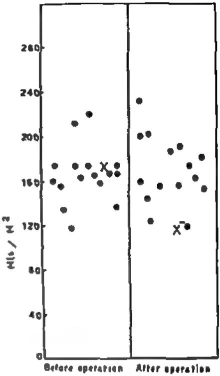

Fig 2 Oxygen consumption before and after operation X Patient 5 X̄ Patient 21 underwent splenectomy 2 years before the shunt operation

with paired observations it averaged 12 25 units and became 7 39 units after the operation with a decrease of 4 86 units (S E 1 3) which is significant at the 5 per cent level (t −3 73)

In the group of patients with unpaired observations the average before operation was 13 56 units and that after it was 8 41 units with a decrease of 5 15 units (S E 1 3) which is also significant at the 5 per cent level (t −3 9)

PULMONARY VASCULAR RESISTANCE (PVR) Before operation the average PVR for the 18 patients studied was 1 33 units (106 dynes) For the 8 patients with paired observations it averaged 1 11 units and became 0 67 units after the operation with a decrease of 0 44 units (S E 0 098) which is significant at the 5 per cent level (t −4 4)

In the group of patients with unpaired observations the average before operation was 1 468 units and that after it was 0 614 units with a decrease of 0 854 units (S E 0 313) which is also significant at 5 per cent level (t −2 77)

WORK OF LEFT VENTRICLE (Fig 5) Before operation the average left ventricular work was 5 34 Kg min /M for the 18 patients studied For the 8 patients with paired observations it averaged 5 8 and became 7 48 Kg min M after the operation with an increase of 1 68 Kg (S E 0 279) which is significant at the 5 per cent level (t +5 8)

In the group of patients with unpaired observations the average before operation was 4 915 Kg min M² and that after it was 6 747 Kg with an increase of 1 832 Kg (S E 0 76) which is also significant at the 5 per cent level (t +2 39)

WORK OF RIGHT VENTRICLE (Fig 6) Before operation the average right ventricular work for the 18 patients studied was 0 88 Kg min M For the 8 patients with paired observations it averaged 0 85 and became 1 15 Kg after operation with an increase of 0 3 Kg (S E 0 145) which is statistically insignificant at the 5 per cent level (t +2 09)

In the group of patients with unpaired observations the average before operation

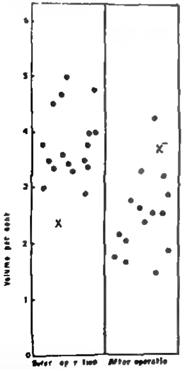

Fig 3 Arteriovenous oxygen difference before and after operation X Patient 5 X¯ Patient 21 underwent splenectomy 2 years before the shunt operation

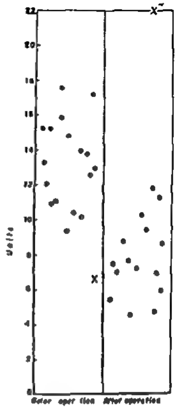

Fig 4 Systemic vascular resistance before and after operation X Patient 5 X¯ Patient 21 underwent splenectomy 2 years before the shunt operation

was 0 904 and became 1 067 Kg after it with an increase of 0 163 Kg (S E 0 244) which is also statistically insignificant at the 5 per cent level (t +0 66)

Discussion

Some patients with advanced Laennec's cirrhosis have a hyperkinetic circulation [6,7] The changes have been attributed to vasodilator substances which reach the general circulation portal hypertension may shunt portal blood rich in vasoactive amines[8] to the general circulation and the diseased liver fails to metabolize them [7] Significant parenchymal insufficiency is always present in these cases which show hyperkinetic circulation This does not apply to bilharzial hepatic fibrosis [9] in which case the liver parenchyma is spared and the liver function is normal or only very slightly disturbed

None of our 18 patients studied before the operation showed clinical signs of a hyperkinetic circulation With the excep

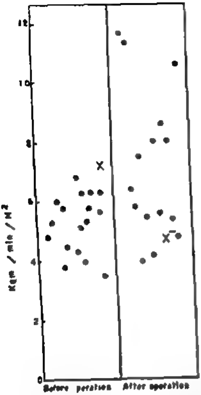

Fig 5 Left ventricular work before and after operation X Patient 5 X⁻ Patient 21 underwent splenectomy 2 years before the shunt operation

tion of Patient 5 all had normal hemodynamic data with the exclusion of Patient 5 the cardiac indices ranged from 2 8 to 5 52 L with an average of 4 22 L — only 1 patient had a cardiac index above 4 [illegible] L These figures are within the normal range of our laboratory as well as the normal range reported by others under the circumstances of catheterization [4,10] As to Patient 5 he had extensive portosystemic collaterals before the operation his estimated hepatic blood flow was low (875 ml per minute) his liver function was relatively disturbed thymol turbidity was 5 units and serum alkaline phosphatase was 15 King Armstrong units Presumably his extensive collaterals were responsible for his high cardiac index and low systemic vascular resistance before the operation The surgical shunt did not add much to his already increased portosystemic communications and thus his circulatory dynamics were unchanged by the operation

After the operation all 16 patients studied with the exception of Patient 21 who had undergone splenectomy 2 years before the shunt operation showed one or more of the clinical signs of a hyperkinetic circulatory state Sinus tachycardia hyperactive apex beat shortened circulation times high pulse pressure due mainly to a lowered diastolic pressure pistol shot sound a Duroziez murmur or capillary pulsations appeared in various combinations early after the operation and continued unchanged throughout the period of observation which extended over several months These clinical signs although definite were not severe in degree

The hemodynamic data after the operation confirmed the fact that the circulation became hyperkinetic Statistical analysis of these data before and after the operation for the groups with paired and unpaired observations furnished combined evidence that the differences were significant at the 5 per cent level The error of reproduci

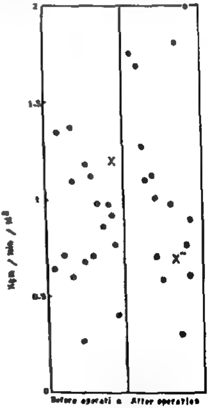

Fig 6 Right ventricular work before and after operation X Patient 5 X⁻ Patient 21 underwent splenectomy 2 years before the shunt operation

bility of the cardiac output by the direct Fick method ranges from 4.5 per cent[11] to 6.2 per cent.[1] The fact that the cardiac index increased while the oxygen consumption was not increased after the operation verifies the fact that the operation created an abnormal circulatory state. The liver function remained intact after the operation. The studies were performed late after the operation (6 weeks to 1½ years) and there was no relation between the circulatory changes and the postoperative date of study. Thus we can safely conclude that the changes in hemodynamics were the direct effect of the surgical bypass.

The operation opened an easy exit for blood from the engorged portal territory; it was delivered directly to the heart short-circuiting the high resistance in the liver. This accelerated and increased the venous return. Subsequently, the cardiac output increased mainly as a result of increased stroke volume; accelerated heart rate was only a contributing factor. There was peripheral vasodilatation as evidenced by decreased systemic vascular resistance; this had perpetuated the increased venous return and both together were responsible for the production of a hyperkinetic circulatory state after the operation. An increase in the blood volume in some of our patients also helped to maintain the high cardiac output. *The augmented blood* volume was due mainly to an increase in the plasma; the resulting lowered viscosity might have contributed to the reduction in the vascular resistances.

The decreased arteriovenous oxygen difference and percentage oxygen utilization coefficient was the result of an increased speed of blood flow past the tissues secondary to vasodilatation and diminished vascular resistance; the tissues satisfied their oxygen need through the repeated passage of a large amount of blood per unit of time by the increased cardiac output and accelerated flow of blood. Oxygen consumption was not altered; the tissue needs were not increased. The hyperkinetic circulation served no useful purpose but was the outcome of the artificial fistula which, although veno-venous, produced the same effects as an arteriovenous fistula, but to a lesser extent.

The effect of increased cardiac output on the ventricular work was partly neutralized by the decreased vascular resistances. The changes in right ventricular work showed a wider scatter than did the changes in left ventricular work (Figs. 5 and 6).

The cardiac volume increased in most of the patients. The increase occurred early after operation and did not progress during the follow-up. It was a physiologic response to a moderate increase in volume load. The pressure in the right atrium and that in the right ventricle, as well as the wedged pulmonary capillary pressure, remained normal.

After the operation the pulmonary flow increased, the pulmonary pressures did not increase, and the pulmonary vascular resistance decreased, which suggests that the pulmonary arterial tree in our patients was healthy and responded normally to the increased flow. In patients with bilharziasis, because of the possible presence of structural involvement of the pulmonary arterial tree, a portocaval shunt operation may lead to arterial pulmonary hypertension; thus it is essential to exclude the possibility of early bilharzial cor pulmonale before advising the operation. Detection of very early cases entails the demonstration of a rise in pulmonary pressure during exercise.[11] This precaution was taken in all the patients studied preoperatively; *none showed a rise in pressure after exercise*, and none showed pulmonary hypertension after the operation, in spite of their return to work which for some entailed heavy muscular effort. Recently, Rodriguez and associates[14] reported that several of their patients with schistosomal liver fibrosis developed clinical signs of bilharzial cor pulmonale after portocaval operation. These patients must have had bilharzial pulmonary endarteritis before the operation, or else intestinal or urinary bilharziasis remained active after the operation and readily shunted ova to the lungs. Thus, it is essential to assure complete cure of bilharzial infection before undertaking a portocaval shunt operation.

Summary

The circulatory hemodynamics were studied before and after a portocaval shunt operation in patients with bilharzial he-

Inverted T waves in the precordial electrocardiogram of normal adolescents

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Sharply inverted T waves in the precordial electrocardiogram have been reported in patients without evidence of clinical heart disease. Inversion of the T waves in Leads V_1 through V_4 have been found so frequently in normal children that it has been called "the normal juvenile pattern." In addition, inversion of the T waves over isolated areas of the precordium (as in V_3 or V_4 areas) have been reported in healthy adults. Inversions of the precordial T waves similar to both of the above-mentioned patterns have been reported in normal adult Negroes[1] as well as in Caucasians.[1,2,9,11] Findings such as these in adults without heart disease have been a source of deep concern because the patterns are alarmingly similar to those often found with acute myocardial disease. No satisfactory explanations have been given for these observations. Some possibilities which have been suggested include the influence of a relative deficiency of potassium,[1,13] the effects of aging,[14] anxiety,[15] fear,[16,17] cooling of the precordial region,[10,18] influence of the intake of food,[19] rotation of the heart in a clockwise position,[9] impact of the cardiac apex against the chest wall,[21] local pericardial or myocardial disease,[21] drinking of ice water,[2] differences in myocardial blood supply,[10] hyperventilation,[11,23,24] sympathetic-parasympathetic imbalance,[10,25] posture,[26,27] the effects of respiration,[28,29] and the influence of local electrical potentials.[30,33]

We have studied the form[34] and the effects of respiration on the T wave.[3] Thus we were interested in finding inverted precordial T waves in the electrocardiogram of a clinically normal adolescent boy. Because of these findings he was prohibited from athletic activities, although he was an outstanding athlete. However, when he took a deep breath and held it, the inverted T waves in V_4 immediately became upright and normal in appearance. The sudden change from an apparently abnormal to a familiar normal-appearing pattern suggested that the changes were not evidence of myocardial disease. Within a short period of time 4 similar cases came to our attention. The following is a presentation of our findings. The factors which may be responsible for the dramatic changes in the ECG are discussed.

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Findings

The clinical features of our 5 cases, summarized in Table I, are within normal limits. Initially all patients had been referred for evaluation of a systolic heart murmur which was found on a routine physical examination at school. Although equal numbers of males and females are seen at our clinic, all of our patients were males. Four were Negroes, two of whom were trained athletes.

The electrocardiographic tracings (Figs. 1-5) show seemingly abnormal inversion of the T waves in V_3 or V_4 precordial leads with "cove planing" of the S-T segments in Cases 2, 3, 4, and 5. The lower tracings were continuously recorded (except in Fig. 4) to show the rapid changes in the tracing when the subject took a deep breath. With this maneuver the seemingly abnormal S-T segments and T waves quickly became normal in appearance. The QRS contour, however, was not significantly changed except for some changes in the voltage. This would seem to indicate that the reversal in the direction of the T waves as a result of the inspiration is not secondary to alterations in the QRS complex.

Discussion

An electrode placed on the precordium is displaced anteriorly and superiorly by the movement of the chest wall on deep inspiration. At the same time the heart is displaced inferiorly as it follows the descent of the diaphragm. This results in a shift in the spatial relations between the precordial electrode and the local area of underlying epicardial surface.

In addition, other changes occur which may be of profound significance. The anatomy of the left lung and reflexions of the pleura are such that an area overlying the anterior surface of the heart is known as "the cardiac notch."[11] Here the anterior surface of the heart is covered by a minimum of lung tissue or none at all (see Figs. 6 and 7). This is normally under the precordial area between V_3 and V_4 electrode positions on the chest. In this region, therefore, the anterior surface of the heart is in closest approximation to the chest wall.[4,5] However, with deep inspiration there is ample room for aeration and expansion of the left lung anteriorly and medially to cover much of the anterior surface of the heart. This removes the heart from its close proximity to the chest wall.

Table I. Summary of clinical features of 5 normal adolescents with inverted precordial T waves

Case	Age (yr.)	Race	Sex	Past history	Performance	BP (mm. Hg)	Murmurs	Fluoroscopy
1. G. T.	18	Negro	M	No cardiac symptoms	Varsity basketball team	100/60	Innocent apical systolic	Upper limit of normal in size; slight prominence of right ventricle
2. J. S.	16	Negro	M	Occasional vague precordial distress	Normal	115/80	Innocent apical systolic	Heart normal in size and shape
3. B. B.	14	White	M	No cardiac symptom	Normal	105/70	Innocent apical systolic	Heart normal in size and shape
4. A. C.	15	Negro	M	No cardiac symptom	Normal varsity track team	130/80	Innocent systolic left sternal border	Heart normal in size and shape
5. F. D.	14	Negro	M	No cardiac symptom	Normal	122/68	Innocent apical systolic	Heart normal in size and shape

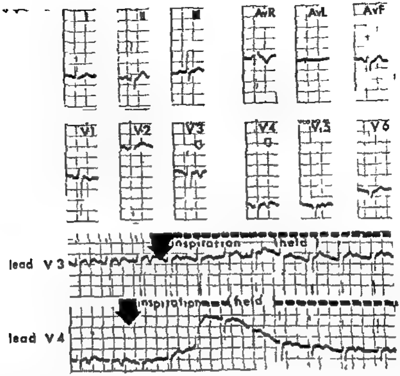

Fig. 3. ECG tracing of a normal 14 year old white boy showing the effects of a deep inspiration upon the contours of the S-T segments and the T waves in Leads V_3 and V_4.

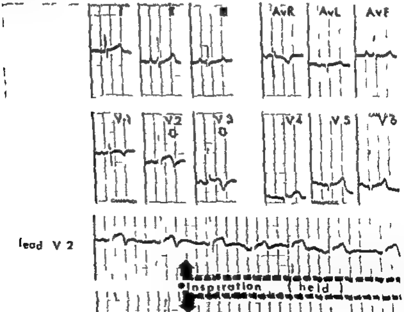

Fig. 4. ECG tracing of a normal 15 year old Negro boy showing the effects of a deep inspiration on the S-T segments and inverted T waves in Leads V_2 and V_3. (The lower tracing is not continuous because of wandering of the base line.)

Fig. 1. The great vessels are closed with stoppers and rubber tubes. The chambers are filled with formalin.

Fig. 2. The windows have been cut in the right atrium, right ventricle, and pulmonary artery. Within the right atrium the coronary sinus and fossa ovalis are seen.

vessels and secured in place by ligatures. All tubes are closed except for that in one of the pulmonary veins and that in the superior vena cava. Through these enough 10 per cent formalin is injected into both sides of the heart to grossly distend the heart and exaggerate the size of the chambers. The open tubes are closed by pinch clamps (Fig. 1). The specimen is then immersed in a container of formalin where it is kept for 3 days.

The heart is then removed from the formalin and the clamps are disengaged. The formalin inside the heart is drained out. The tubes are removed and the specimen is washed with water.

A right atrial window is prepared by a section into the right atrium anterior to the venae cavae. The incision is extended to the atrium superiorly and inferiorly. This window allows for visualization of the intrinsic structures of the right atrium including the septum, foramen ovale, coronary sinus, and tricuspid valve (Fig. 2).

A finger is placed into the right ventricle through the tricuspid valve to guide the next cut. A section is made into the outflow tract of the right ventricle but not into the pulmonary valve. This incision is enlarged laterally by successive contiguous cuts to allow for inspection of the right ventricle, including the papillary muscles, ventricular septum, crista supraventricularis, and the pulmonary valve (Fig. 3).

The pulmonary artery is opened by removing an elliptical segment of the anterior

Fig. 3. Through the window in the right ventricle a ventricular septal defect is seen, bounded anteriorly by the crista supraventricularis. The papillary muscle of the conus inserts into the superior edge of the defect.

wall The pulmonary valve is seen through this window

The left atrium is opened through two areas The first is a small orifice below the orifices of the pulmonary veins A second section unroofs the atrium (Fig 4) If these windows are joined the wall is likely to collapse This may be remedied by placing cotton in the chamber during the clearing and imbedding stages

The left ventricle is opened along the anterior wall The first incision is made parallel to the septum as seen through the right ventricular window (Fig 5) This section is carried up to but not into the aortic valve The size of the window is increased by parallel sections lateral to the first Care must be taken to prevent damage to the papillary muscles of the mitral valve

The aorta is opened in a manner similar to the pulmonary artery The specimen is now ready for a complete gross description Portions of the tissue removed in the preparation of the windows are now appropriately labeled and prepared for histologic examination

Processing is now continued through alcohol xylene and paraffin These solutions are contained in a series of eight bottles as follows (1) 80 per cent alcohol (2) 80 per cent alcohol (3) 95 per cent alcohol (4) 95 per cent alcohol (5) absolute alcohol (6) absolute alcohol (7) xylene (8) xylene The specimen is kept in each solution for 24 hours After being processed through the second xylene the specimen is imbedded in two paraffin baths at 60 C for one day each After this the excess paraffin is drained off and the specimen is placed in the refrigerator (4 to 10 C) for 2 to 3 hours for hardening Excess paraffin may be trimmed away

Discussion

There are several advantages to this method A major one is that intracardiac defects with anatomic relationships closely approximating those existing during life can be seen Malformations of the atrial septum atrioventricular valves the ventricular septum and the semilunar valves are readily identified

Anomalous venous connections may be preserved by maintaining continuity of the affected adjacent structures including lung or other viscus with the vascular attachments through the entire process

The paraffin embedded specimen may be kept in a box on a shelf with consider

Fig 4 Two windows have been opened into the left atrium (The multiple small holes in the ventricle are artefactual from a multipointed structure used to hold the heart for photographs)

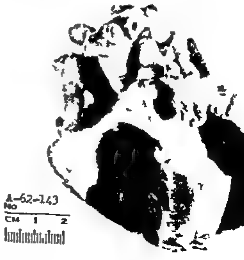

Fig 5 The left ventricular window is along the anterior segment of the ventricle A surgically placed band had been put about the pulmonary artery The ductus had been surgically ligated

able saving in storage space There is also the obvious advantage of ready accessibility for comparison with other specimens Absent are the annoying features of formalin soaked fingers and formalin fumes

A major disadvantage of the paraffin embedded specimen is the shrinkage which occurs when the specimen is placed in paraffin The general volume decreases by 20 to 30 per cent when the specimen leaves the second xylene bath and is placed in the paraffin Attempts at using other methods of fixation including water soluble waxes have been unsuccessful For this reason a specimen with a total weight of 75 grams or less is rarely processed beyond the formalin fixed stage The preliminary process of distention fixation and creation of windows is carried out The specimen is then kept in formalin This maintains the advantage of the intact specimen but also maintains the disadvantage of wet preservation

Another major difficulty is caused by the structure of the left ventricle in the region of the aortic valve The left ventricle is opened along the anterior edge where the mitral valve can readily be seen and its structure evaluated but the ventricular aspect of the aortic valve is frequently difficult to define To overcome this disadvantage the aorta may be dissected down to the base so that the aortic valve can be seen from the aortic aspect

Summary

A method has been described for fixation and preservation of congenitally malformed hearts to retain the basic anatomic configuration The advantages include retention of normal relationships for study and demonstration Also a major advantage is that the specimen may be stored dry

Major disadvantages include shrinkage of the specimen in paraffin and an occasionally unsatisfactory evaluation of the left ventricular aspect of the aortic valve

Reliable extrapolation of indicator-dilution curves without replotting

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In keeping with the relative ease and rapidity with which cardiac output can be calculated by the isotope precordial counting and dye densitometer methods, the indicator dilution curves are recorded directly in linear coordinates. Before the area of a curve can be computed with a polar planimeter and used in the formula for cardiac output, it must be extrapolated from the start of recirculation to the preinjection base line in an exponential manner.[1-8] At present this is accomplished with consistent accuracy only by tedious and time-consuming point by point plotting of each curve's downslope on semilogarithmic coordinates, extension of its straight line form with a ruler, and replotting of this extrapolation on the original rectilinear graph.

The purpose of this study was to evaluate a simple and inexpensive device by which reliable and accurate exponential extrapolation of directly recorded indicator dilution curves can be quickly performed *without replotting*.

Method

A set of truly exponential curves embracing a variety of downslopes likely to be encountered in human cardiac output curves has been designed to serve as an underlay beneath rectilinear charts on which indicator-dilution curves have been inscribed. With the common base level of the set of exponential curves aligned with the preinjection base line of an inscribed curve, one can quickly select, by sliding the record along the underlay, the exponential curve which matches the inscribed part of the downslope (Fig. 1). Significant deviation of the inscribed part from the exponential decrease can then be identified as the start of obvious recirculation, and correct extrapolation can be quickly accomplished by tracing with a pencil the rest of the exponential curve on the rectilinear chart paper.

In the design of this device, each curve of the set represents log $v = kt$. The vertical scale v was made arbitrary but common to the entire set. The origin of the horizontal time scale (t) was moved over slightly for each curve in order to avoid overlap. The constant k describing the shape or downslope or time constant of a given curve was changed from curve to curve by small increments to provide the desired variety. The set can be used with any width chart so long as the downslope falls within the range of the set. Although a set of *exponential* curves may be constructed by plotting for each curve many

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points from a log table the illustrated set was produced by an analog computer solution of $y = ky$ on an X-Y plotter set ting k for each curve by a simple turn of a potentiometer

To evaluate the accuracy and reliability of this device it was used for the extrap olation of 25 cardiac output curves In each case the calculated cardiac index value was compared to respective values calculated after extrapolation of the same

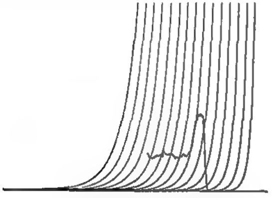

Fig *1* Set of exponential curve used as guide for extrapolation of indicator-dilution curves recorded directly on rectilinear paper The recorded curve is placed over exponential curves which can be ob served through rectilinear paper and is moved hori zontally until superimposed on the exponential curve which best matches the inscribed down lope as shown Exponential extrapolation from the start of obvious recirculation is then traced on rectilinear graph

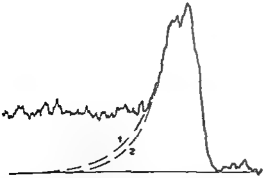

Fig *2* Patient J M Feb 14 1961 Precordial dilu tion curve which illustrates occasional possibility of two extrapolations from two exponential curve both of which match the inscribed down lope The basic problem is that superimposed random fluc tuations can cause difficulty in discerning the start of obvious recirculation The cardiac index value using extrapolation *1* was 3 47 L/min/M² or extrapolation *2* was 3 58 L/min/M²

output curve by (1) semilog plotting of the inscribed downslope extrapolation by extension of the straight line replotting of this extension on the original rectilinear chart and (2) direct extrapolations by visual inspection and several reasonable placements of a French curve

The 25 cardiac output curves extrap olated by three different techniques were recorded from consecutive patients who ranged in age from 27 to 54 years from 1 77 to 2 12 M² in body surface area and from 5 020 to 7 130 ml in total blood volume The group included several with cardiac disease Cardiac index values de termined at rest (supine) or during per formance of bicycle exercise (sitting) varied from 2 61 to 7 33 L/min/M²

Iodinated (I^{131}) human serum albumin (10 to 20 μc) was injected via an antecubital vein and scintillation counting was per formed over the precordium in all cases with the same sensitivity and time con stant settings as described previously[8] Therefore variations in curve area peak concentration and angle of downslope were caused mainly by differences in cardiac output and intracardiac blood volume

Results

Table I summarizes the results of using the three different extrapolation techniques In comparisons of cardiac index values cal culated with extrapolation by semilog plotting and by guidance from the set of ex ponential curves the greatest difference was 0 09 L/min/M² In all but 5 of the 25 output curves the pairs of values corre sponded exactly or within 0 02 L/min/M²

On the other hand use of visual inspec tion of the inscribed curve and proper placement of a French curve to guide the direct extrapolation is fraught with con siderably greater potential error Using semilog plotting again as a standard com parisons for each curve with extrapolations along a range of several reasonable place ments of a French curve revealed cardiac index values as much as 0 38 L/min/M² too low and 0 51 too high Arithmetic means for the greatest reasonable errors in placement of the French curve were 0 16 L/min/M² on the negative side and 0 21 for erroneously high cardiac index values

In extrapolations of approximately 500

Table I

Patient	Status	Cardiac index (L/min/M²)			Difference (1 minus 2)	Difference (1 minus 3)	
		1 Semilog plotting	2 Set of exponential curves	3 French curve (range)		Low	High
E H	Supine resting	4.17	4.22	3.95–4.46	+0.05	−0.22	+0.29
R E	Supine resting	3.52	3.61	3.31–4.03	+0.09	−0.21	+0.51
R M	Supine resting	4.30	4.30	3.92–4.49	0.00	−0.38	+0.19
	Sitting exercising	7.33	7.34	7.15–7.38	+0.01	−0.18	+0.05
H H	Supine resting	3.48	3.48	3.29–3.81	0.00	−0.19	+0.33
	Sitting exercising	4.99	5.04	4.95–5.15	+0.05	−0.04	+0.16
D C	Supine resting	4.60	4.60	4.51–4.73	0.00	−0.09	+0.13
	Sitting exercising	5.67	5.67	5.58–5.70	0.00	−0.04	+0.[illegible]
E H	Supine resting	2.83	2.85	2.56–3.25	−0.02	−0.27	+0.42
A K	Supine resting	3.20	3.20	3.04–3.29	0.00	−0.16	+0.09
	Sitting exercising	[illegible].04	6.04	5.91–6.11	0.00	−0.13	+0.07
S C	Supine resting	3.97	3.96	3.88–4.02	−0.01	−0.09	+0.05
C M	Supine resting	4.08	4.09	4.00–4.17	+0.01	−0.08	+0.09
E S	Supine resting	3.27	3.29	3.25–3.48	+0.02	−0.02	+0.21
H L	Supine resting	3.13	3.11	2.90–3.57	−0.02	−0.23	+0.44
R G	Supine resting	3.36	3.33	3.23–3.54	−0.03	−0.13	+0.18
	Sitting exercising	5.80	5.80	5.68–5.98	0.00	−0.12	+0.[illegible]
L S	Supine resting	4.07	4.07	4.00–4.18	0.00	−0.07	+0.11
E H	Supine resting	2.93	2.93	2.89–3.11	0.00	−0.04	+0.18
J M	Supine resting	4.00	3.99	3.65–4.18	−0.01	−0.35	+0.18
W B	Supine resting	4.13	4.13	4.00–4.19	0.00	−0.13	+0.06
A S	Supine resting	2.65	2.72	2.42–3.10	+0.07	−0.23	+0.45
R M	Supine resting	4.08	4.10	3.85–4.47	+0.02	−0.23	+0.39
J S	Supine resting	4.27	4.28	4.18–4.57	+0.01	−0.09	+0.30
	Sitting exercising	5.54	5.56	5.29–5.65	+0.02	−0.25	+0.11

external counting curves the time saving features of the device herein described as opposed to semilog plotting were constantly recognized. It was considered helpful to design two sets of exponential curves one set to cover the range of slopes of the majority of patient curves and another set—with a greater difference between adjacent exponential curves—to extend over the entire variety of slopes likely to be encountered. In this way the possible error of having a patient-curve downslope fall between two of the model curves was further reduced yet the variety of downslopes encountered in this group of patients could be accommodated.

On rare occasions difficulty occurred in choosing which one of two curves matched more appropriately the downslope of an inscribed curve (Fig. 2). These instances were caused usually by the superimposition of a random fluctuation on part of the downslope. (This was a somewhat more frequent problem with the use of shorter time constants.) When related to the total curve the difference in area using the two possible extrapolations was usually minor. Replotting of such curves on semilog graphs did not help in deciding on the more applicable extrapolation.

Discussion

The basic accuracy of the precordial counting technique as evaluated with glass models and by comparisons with simultaneous dye arterial sampling or Fick principle techniques has been previously covered as have been the particular advantages and limitations.[7, 15] The focus in this study was on the mode of exponential extrapolation of the primary circulation curves past the onset of recirculation.

It has been well recognized that the washout part of the indicator dilution

curves does not always follow exactly an exponential decline. However, deviations are relatively minor and have not detracted over the years from the usefulness of exponential declines in guiding extrapolations with reasonable accuracy.[12,14]

In most laboratories exponential extrapolation of directly recorded isotope or dye dilution curves is accomplished by tedious point for point replotting. While of sufficient accuracy and reliability, this part of the calculation of cardiac output requires an extra 20 to 30 minutes per curve.

Recently analog computing devices for automatic exponential extrapolation and computation of curve area have been announced. These are necessarily expensive and require extensive evaluation before one can rely on their accuracy in a wide variety of curves.

Some workers, after acquiring considerable experience in extrapolating curves of the same general size and shape, have learned to select the start of recirculation and to draw the exponential downslope by visual inspection and the help of only a French curve. Because of the time saved (by omitting the semilog plotting), workers in some laboratories have been tempted into adopting this "eyeballing" technique as routine procedure. Unfortunately, interpretation and extrapolation by visual inspection alone can be shown at times to result in marked deviation from the actual corresponding exponential downslope. In addition, it can lead to considerable variation in extrapolation by different workers faced with calculation of cardiac output from the same indicator-dilution curve. Therefore, this mode of extrapolation is considered to introduce a potentially significant source of error to the precordial counting procedure.

The device described and evaluated in this report is thought to combine the advantages of the above-mentioned procedures. Analysis and calculation of approximately 500 indicator-dilution curves over a period of 2 years has indicated the usefulness of this device in a laboratory in which cardiac output is determined mostly by the isotope precordial counting technique. It might be easily adapted also to direct rectilinear recordings of dye-dilution curves. In theory, use of this time-saving device should match the accuracy of semilog plotting of the inscribed part of the dilution curve and replotting of the extrapolation back to the rectilinear graph, because in effect this is how the set of sample curves was constructed. Its degree of accuracy, using semilog plotting as the standard, seems acceptable on the basis of the data summarized in Table I. If one has access to a simple analog computer and X-Y plotter one time, this device can be quickly and reasonably constructed. It will obviate the temptation to save time by the use of only visual inspection and a French curve in extrapolation of indicator-dilution curves.

Summary

A device for simple, rapid, and accurate extrapolation of directly recorded dye or isotope dilution curves has been described and evaluated. A set of exponential curves was constructed to serve as an underlay for rectilinear recordings of dilution curves and in this way to guide reliably in the proper extrapolation of many and varied curves. This technique was found to match the accuracy of the tedious and more time-consuming semilogarithmic plotting of inscribed downslopes. It will obviate the temptation to select the start of recirculation and to extrapolate past this point by visual inspection.

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The electrocardiogram of a baby elephant

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The electrocardiograms of adult elephants have been recorded by Forbes and associates[1] White and associates[2] and Jayasinghe and Brito Babapulle[3] Their work was limited to recordings from only the limb leads

Now using not only limb leads but also lateral chest leads we have had the opportunity of recording the electrocardiogram of a baby elephant

Material and method

The baby elephant belonging to the species *Elephas maximus* found in the jungles of Ceylon was captured and brought to the Zoological Gardens Dehiwala She was 3 feet in height 1 year old and black colored with hardly any areas of depigmentation

The equipment used was a Sanborn Viso Cardiette 52 The speed of the paper was 25 mm per second and the sensitivity of the instrument was calibrated at 1 5 cm = 1 millivolt Crocodile clip electrodes were attached to the skin of the axilla and groins Redux electrode jelly was rubbed into the skin at these sites before the electrodes were attached

The animal remained perfectly quiet when the keeper gently scratched its fore

Table 1 Electrocardiographic time intervals of the baby elephant

Lead	P (sec)	P R (sec)	QRS (sec)	Q T (sec)	T (sec)	Rate per minute
I	0.08	0.29	0.08	0.61	0.36	36
II	0.09	0.32	0.09	0.64	0.44	37
III	0.08	0.28	0.08	0.64	0.44	37
aVR	0.08	0.28	0.08	0.60	0.40	38
aVL	0.08	0.28	0.08	0.60	0.40	39
aVF	0.08	0.28	0.08	0.60	0.40	39
CV,RL	0.08	0.28	0.08	0.62	0.40	39
CV,LL	0.09	0.28	0.08	0.60	0.32	37
CV LL	0.09	0.28	0.09	0.60	0.40	36
V	0.10	0.29	0.10	0.64	0.40	38

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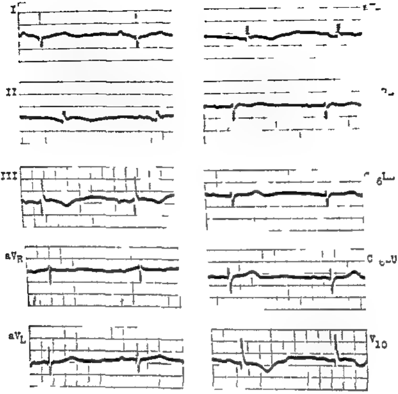

Fig 1 Electrocardiogram of the baby elephant

head and intermandibular areas No drugs were given to restrain the animal at any time

Results

P wave The average duration of the P wave was 0 08 second and the average amplitude was about 0 1 millivolt

P R interval The P R interval averaged 0 28 second and the QRS complex averaged 0 08 second The QRS complex was tallest in Leads I III and V_{10}

The duration of the T wave averaged 0 40 second These waves were prolonged and dome shaped

The duration of systole (Q T interval) varied from 0 60 to 0 64 second and the average heart rate was 37 beats per minute

Discussion

Our results were characterized by the large and clear excursions of all the electrocardiographic complexes (P Q R S and T) This is in marked contrast to the earlier recordings[1,2] which were of low amplitude Various explanations were given such as the thickness of the skin the [illegible] electrodes applied the great distance [illegible] electrodes from the heart [illegible] different models of recordin[illegible] used in the other studies

It seemed reasonable to [illegible] clarity of the electroc[illegible] in the baby elephant [illegible] relatively low resistance [illegible] thinner skin of this [illegible] nection the work of [illegible] cattle and horses showed [illegible] of the skin could be [illegible] determining the [illegible] cardiographic compl[illegible] plate type surface [illegible] tudes were much [illegible] needle electrodes [illegible]

This work sug[illegible] tudes in adult [illegible] increased thick[illegible] mal grows older

Summary

The electro[illegible] was recorded [illegible]

number of lateral chest leads For all electrocardiographic complexes amplitudes larger than those in the adult have been obtained The heart rate in the standing position was 37 beats per minute

We wish to thank Mr Lyn de Alwis Director Zoological Gardens of Ceylon and the zoo veterinarians Dr W W Dennis Fernando and Dr C Meemaduma for their cooperation

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Case report

Atrioventricular nodal (reciprocating) rhythm

Report of a case

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The occasional occurrence of retrograde activation of the atrium when premature ventricular contractions are initiated by a nodal (or ventricular) pacemaker has been recognized since the reports of White[1] and Drury [2] This retrograde activation in turn may reactivate the ventricle (a reciprocal beating) Kistin[3] has recently reviewed the phenomena emphasizing the viewpoint that the interpolation of many ventricular premature contractions was the overt manifestation of multiple pathways of atrioventricular (A V) conduction and reciprocation The occurrence of reciprocation in sequence to a beat of sinus (or atrial) initiation and propagation has been under disputation but it may occur as exemplified by the case described by Soloff and Zatuchni [4] and the term reverse reciprocal rhythm has been applied

The case report by Moe and associates[5] of reciprocal rhythm in the dog under conditions simulating sinus node destruction—an electrically paced atrium into which is introduced a specifically timed early atrial stimulus—has shown that reciprocation can follow an atrial pacemaker The reasons for believing that the patient whose case is reported herein had a reciprocal rhythm as a basic mechanism rather than isolated nodal premature systoles with orthograde block and episodic nodal tachycardia are the main points of interest to be stressed

Report of case

The patient a 44 year-old woman was seen first in June 1962 because of palpitation and a history of heart failure The features that seemed to be pertinent to the arrhythmia were a history of life long paroxysmal tachycardia an early electrocardiographic pattern showing the Wolff Parkinson White syndrome (Fig 1) a thyroidectomy in 1956 followed by myxedema and frank heart failure in 1959

The first electrocardiographic studies were made over a period of 3 weeks in June and July 1962 The patient was myxedematous and had a large pericardial effusion The tracings showed prolonged sequences of tachycardia of an R P nodal variety interposed with periods of bradycardia only rarely did a heartbeat follow an atrial pacemaker There was essentially no difference between the results of studies made when the patient was being given digitalis and those made 3 weeks after this therapy was stopped Medical management was difficult but on treatment with 0 2 mg of levothyroxine (Synthroid Sodium) daily she became euthyroid and the pericardial effusion disappeared This was her general status when she was restudied in March 1963 (Fig 2) The main problem was still the arrhythmia

In review the pertinent features of the case in respect to the arrhythmia were paroxysmal tachycardia in early life pres

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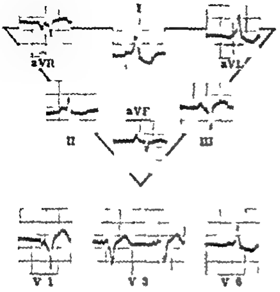


Fig. 1. Electrocardiogram recorded in 1955 showing the W. P. W. (Parkinson-White) syndrome.

ence of pre-excitation (Wolff-Parkinson-White) syndrome many years before the current arrhythmia problem, presence of right bundle branch block, and severely reduced automaticity of any atrial pacemaker. After periods of asystole an atrial pacemaker (possibly sinus) occasionally made its debut, but the automaticity of any atrial focus was poorly sustained (Figs. 3, 4, 5 and 6). Such indolent activity over many months of observation suggested that there was destruction of the sinus node or blocking of its impulse.

The most stable rhythm was a tachycardia with a rate of 130 to 140 per minute which gave the appearance of a nodal tachycardia of the R-P type, but which seemed to be consistent with a reciprocal rhythm with a P-R interval of approximately 0.25 second and an R-P of 0.20 second. In so far as frequent monitoring could reveal, this tachycardia was present most of the time during a period of 8 months (Fig. 2).

In both periods of study, 8 months apart, the tachycardia was consistently but transiently stopped by pressure on either carotid sinus. The resumption of the ventricular beat was due either to an atrial pacemaker with a P-R interval or a nodal pacemaker with an R-P period. Occasionally, the returning atrial and ventricular beats were independent, each being stimulated separately from an atrial and a nodal center, respectively (Fig. 5). Usually the beats engendered by the atrial pacemaker were followed by an atrial echo; however, occasionally in short sequences of atrial beats the first beat of the sequence did not have an atrial echo but the subsequent beat(s) did (Fig. 4). Almost always when the returning beat was nodal in origin the QRS had the same configuration as the sinus beat, namely, right bundle branch block, indicating that the ventricle was excited by a stimulus propagated through the left bundle whether the rhythmic focus was atrial or in junctional tissue. On rare occasions the QRS of the returning cycle from nodal stimulation had a left bundle branch block configuration, indicating that excitation was possible through the right bundle with permission of prompt retrograde excitation to the atria as before.

The sensitivity of the tachycardia to vagal influence, which response was abolished by 1/100 grain of atropine given intravenously, can be interpreted as related either to suppression of a reentrant impulse on its way to the ventricle or to suppression of a rapid nodal cycle; the former concept is favored. Such a test does not discriminate between the two conditions.

The slight increases in rate with the administration of atropine 1/100 grain intravenously and with isoproterenol (Isuprel) 15 mg. sublingually were of the same magnitude, and slight decreases in cycle length were obtained from the P-R interval; the R-P interval remained constant, but such measurements have considerable latitude for error.

The terms "P-R" and "R-P" periods used herein refer to measured intervals on the graphic record and per se do not imply a reciprocal beating of the atria and ventricles. The measurements necessarily are made in an arbitrary way, the most precise being from the Q wave to the intrinsicoid deflection of the P wave in the esophageal trace, which occurs late in the inscription of the P wave.

The tachycardia sometimes was terminated by slight increments in P-R interval suggesting an orthograde Wencke-

bach phenomenon (Fig 3) It is recognized that a nodal pacemaker could decrease its rate before cessation

The tachycardia was terminated occasionally by a QRS of left bundle branch block configuration (Fig 3) and the atrial echo occurred earlier than in the previously stereotyped response after the right bundle branch block configurations

In the presence of the tachycardia the P P intervals varied little from 0 44 second When there were sinus (atrial) beats the interval between the P of atrial origin and the P presumably related to retrograde

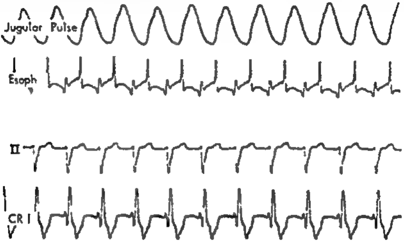


Fig 2 Electrocardiogram and jugular pulse showing the persistent tachycardia present for the major part of the time during which the patient was under observation

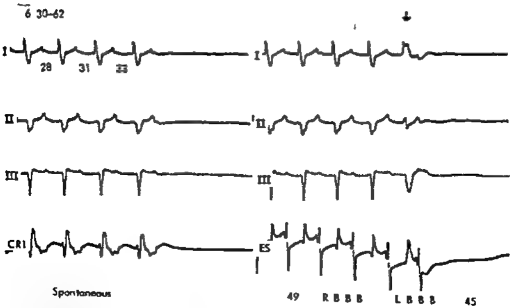
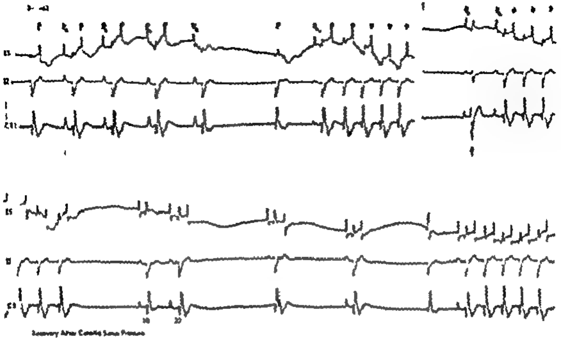


Fig 3 Electrocardiogram recorded when the patient was myxedematous illustrating types of cessation of the A V nodal rhythm *Left* Slowing of the rate with the increase in cycle length being in the P to R duration the R P remains constant *Right* A decrease in atrial cycle (0 49 to 0 45 second) related to a shortening of the period associated with a QRS configuration of a left bundle branch block type



4. Electrocardiogram records 18 months after tracing seen in Fig. 3 show various phenomena of A-V conduction. In the upper left panel is a sequence of four beats with a single pacemaker with an atrial echo in the first three; with the fourth beat the P-R interval is slightly shorter and no sequential atrial beat occurs. On the tachycardia following an atrial focus beat, but the different P wave configuration shows that the pacemaker is at a different location. At the arrow in the upper right panel there is a beat apparently initiated in the atrium with a single QRS of the left bundle branch block type. The lower panel illustrates a common occurrence with sequences of atrial bigeminy bracketing a QRS. In the grouping left of center the first recovery beat of atrial pacemaker origin has a shorter (0.18 second) P-R interval (and no sequential P wave) than the next beat (0.22 second) which is followed by an atrial echo.

conduction was 0.36 second. If one preferred the theory of a nodal rhythm, one would have to explain a more rapid nodal cycle at these times, perhaps by postulating either a protective entrance block of the active nodal focus from the anterograde impulse or initiation of the nodal firing by a mechanical effect of the ventricular contraction. A dual pathway with reciprocal atrial echo would seem to be the more attractive hypothesis.

At the time of re-establishment of tachycardia the first R-P interval was often longer by 0.04 second than it was in subsequent beats. On resumption of the tachycardia, the initial complexes were either of an atrial (P-R-P) or nodal (R-P) form and occasionally, with simultaneous independent atrial and nodal pacing, the P wave of the atrial form was superimposed on the QRS (Fig. 6).

Occasional sequences of several beats of the R-P type showed variation in the cycle length; the corresponding rates were 38 to 46 per minute, an automaticity which one is accustomed to associate with a junctional (or nodal) pacemaker. Other sequences of bigeminy commonly were observed in which the second beat had a P wave following the QRS (a P-R-P-R-P sequence), and the retrograde excitation always then suppressed the atrial pacemaker for about 1.3 seconds. In these sequences, the second P-R always exceeded the first by approximately 0.04 second—the P-R increasing from 0.18 to 0.20 second to 0.22 to 0.24 second (Fig. 4). Such a sequence of two atrial beats with a P-R increment in the second sometimes preceded a resumption of the tachycardia. These phenomena are interpreted as a subsequent retrograde excitation with an atrial echo.

The actual presence of true reciprocating rhythm, presumably related to a double atrioventricular (A-V) conduction path

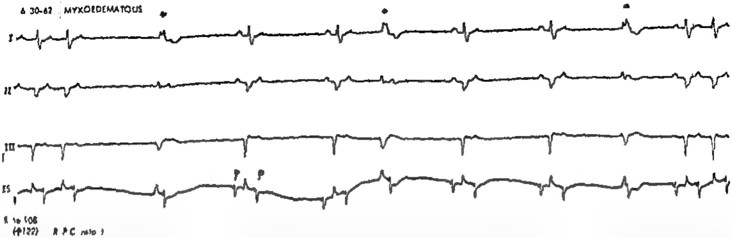


Fig. 5 Period of temporary cessation of A V nodal tachycardia (at both ends of the tracing) showing the atrial bigeminy. Three beats (*) show nodal beats with a QRS of left bundle branch block configuration. *In that complex to the right the ventricle follows the nodal pacemaker* and the atrium follows the atrial pacemaker almost simultaneously. When tachycardia was present the rate varied from 109 to 122 *with the R-R interval remaining constant*.

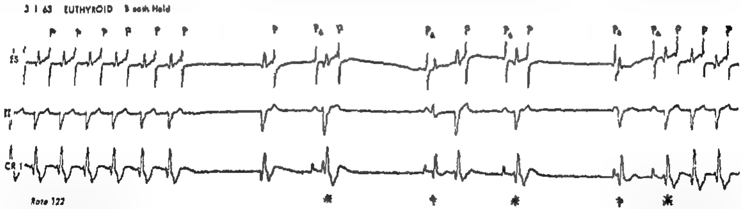


Fig. 6 Electrocardiogram recorded 8 months after that seen in Fig. 5 *shows* a period of temporary cessation of A V nodal tachycardia. P waves from an atrial pacemaker are designated *P* and those of retrograde origin *P_A*. The sequences showing the apparent atrial re-entry are marked with an asterisk (*). The QRS sequences marked with a double dagger (‡) *have nearly simultaneous* atrial and ventricular beats from independent atrial and ventricular pacemakers.

was an instance of A-V nodal rhythm is difficult to identify positively. Reciprocation is not always present in A-V nodal rhythm, and convincing demonstration of this is the Group III of Pick, Langendorf, and Katz[6]—A-V nodal tachycardia with forward block in the presence of retrograde conduction. Figure 5 in their paper is particularly pertinent: there clearly appeared to be Wenckebach periods of both forward and retrograde conduction with a nodal rate of 167 and a 5 to 4 conduction to the ventricles and a 5 to 3 conduction to the atria.

Dreifus and co-workers[7] have re-emphasized the etiological role of digitalis in A-V nodal rhythm, and in the well-studied case of reciprocal beating reported by Pick and Langendorf the patient had had digitalis which was presumed to play some etiological role in the arrhythmia. The patient whose case is reported herein had had varying doses of digitalis without overt effect, and on the first occasion for study she had no basic change in the rhythm after not having had digitalis for 3 weeks. However, the impression was that episodes of more rapid tachycardia (160+) (which was not observed by me) were modified or prevented.

The persistence of tachycardia in this case is particularly noteworthy. The cycle length of 0.45 to 0.50 second is in the exact range of the values for the cycle length observed in numerous studies of the coupling of reciprocal beats and for which the time intervals for anterograde and retrograde conduction have been estimated by Pick and Langendorf.[8] The case of paroxysmal tachycardia reported by Naum[9] bears a close resemblance to the case reported herein. The electrocardiograms that he reported show short sequences of reciprocation, a P R P′ R P_x sequence (the x_1 and x indicate an atrial extrasystole). The R-P periods were remarkably constant and the cycle of the tachycardia (0.42 second) was similar to that in the case reported herein.

Summary

Electrocardiograms of a patient showed (a) evidence of atrial echo beats following a ventricular beat initiated by an atrial pacemaker and (b) long periods of apparent atrioventricular (A-V) nodal rhythm consistent with reciprocal atrioventricular beating. The atrial pacemaker activity was poorly sustained and was associated with slight prolongation of the P-R interval when atrial re-entry occurred. A right bundle branch block was present, and a Wolff-Parkinson-White syndrome had been observed in an electrocardiogram of this patient several years previously.

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On the integration of factors in essential hypertension

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Recent investigation of basic mechanisms in human hypertension have provided us with a number of facts and phenomena which up to the present time seem to defy attempts at interrelation. It might be the better part of valor to let these phenomena stand as unrelated, at least at present. We believe, however, that attempts at integration are justified even if they eventually prove to be incorrect in part. Such theories or hypotheses determine directions for future research.

We propose, therefore, to list the phenomena referred to and ask questions concerning their interrelationships and then examine the possible answers. Some of these phenomena will be those which have occupied attention in our own laboratory, whereas others will be culled from the experiences of other workers.

The major questions which demand answers might be posed as follows:

1. What is the hereditary abnormality which determines the development of essential hypertension and how is it transmitted?
2. What is the relationship of the catecholamines to this hypertension?
3. What is the relationship of sodium metabolism to the complex?
4. Can we determine the role played by the renin angiotensin system?
5. Why is therapy successful or unsuccessful in decreasing blood pressure?
6. What is the relationship between hypertension and arteriosclerosis? hypertension and diabetes mellitus? hypertension and renal disease?

The exact hereditary abnormality in hypertension has not as yet been characterized. The controversy as to whether it is multifactorial or unifactorial,[1] based on incidence distribution in populations, is not resolvable on a statistical basis. Limiting his observation to age groups 45-60, Platt has demonstrated that the distribution is bimodal, but this problem will not be solved until identification of the trait within a chromosome becomes possible. The identification of a gross chromosomal abnormality seems unlikely, but chemical analysis of chromosomes and their genes by radioactive labeling of DNA and RNA[2] and the extension of such methods give some promise toward eventual identification of the genetic abnormality responsible for the substrate of essential hypertension.

It is not understood how such an abnormality determines the chemical change responsible for the development of the disease, but if other patterns are followed, one may presume that the chromosomal change determines a structural change in

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one or more proteins,[4] possibly enzymatic in character. The nature of these proteins will be discussed further, but first let us ask what is transmitted in physiologic terms.

Elevation of the systemic blood pressure is a physiologic response to the constriction of systemic arterioles, and this constriction is produced by the contraction of smooth muscle cells. These smooth muscle cells contract for the most part in response to stimulation by sympathetic nerves which release the effector substance, l-norepinephrine (NE).[5] It has been shown by us and other workers that essential hypertension is characterized by increased responsiveness of the systemic blood vessels to stimulation by NE,[6] or in fact to stimulation by many vasoactive substances,[7] rather than characterized by increased release of the effector substance NE. This has been demonstrated for skin[8] and for striated muscle,[8] but not thus far for visceral structures, such as the kidney.[9] This hyperresponsiveness is, in fact, the earliest manifestation of essential hypertension and may even be demonstrated in the nonhypertensive children of hypertensive parents.[10] The hyperreactivity is brought out especially after sympathetic neural blockade,[6,7] and therefore is probably not a reaction within the central nervous system.

That such hyperreactivity is not caused by structural changes in the blood vessels is indicated by normal vascular responsiveness to vasoactive substances in Raynaud's disease and in renal hypertension, as well as by the rapidity with which changes in responsiveness can be produced by steroids.[11] Recent experiments which suggest that increased responsiveness may be attributed to increased vascular "stretch"[1] by the hypertension are inconsistent with a rectilinear flow pressure slope with increasing pressure. Increased stretch should produce convexity of this relationship toward the pressure axis as well as increased rather than the observed normal responsiveness in renal hypertension.

We may now examine the second question, namely, what is the exact relationship between the catecholamines and essential hypertension. That such a relationship exists seems obvious since nearly all antihypertensive medication aims at decreasing the amount of released NE available for stimulation of smooth muscle,[13,14] and no one today will aver that such therapy is not effective, at least in reducing the blood pressure. Some may argue that these drugs act chiefly on the venules and thus decrease venous return and cardiac output,[15,17] but most observations indicate that arterioles as well as venules are affected,[18,19] and that the diminution in cardiac output is more of a factor in acute experiments than after long-term use of these drugs.[20,21]

Yet every effort at demonstrating any change in NE metabolism in essential hypertension has thus far failed. Urinary catecholamines, vanillylmandelic acid (VMA),[3] and other metabolites[22] are normal in hypertension. One may argue that there might be differences between diurnal and nocturnal excretion,[3] or that the blood vessel effects are obscured by metabolism that takes place in the liver, but the road signs point away from any obvious deficiency in the degradation of NE in essential hypertension. We were among the first to suggest such a deficiency, chiefly in the enzyme catechol-O-methyl transferase, as a cause for hypertension,[23] but unless such a deficiency is confined to the walls of the blood vessels and is absent in the liver, which seems unlikely, it is clear that the hypertensive subject is quite capable of O-methylation as well as of amine oxidation of his NE.

How then are we to explain the increased reactivity to NE in the subject with essential hypertension? If one leaves aside an abnormality in catabolism for the time being, the two other explanations are (1) an increase in intrinsic responsiveness of smooth muscle because of a chemical or structural change in the muscle itself, or (2) a change in the distribution of stored and free NE on infusion, less going into the stored form than remaining free. It is possible, in fact in our view even likely, that both these mechanisms come into play. The question is in what order?

The first clue that an abnormality in metabolism of vasoactive substances might be involved in hypertension came from an unexpected source. It was found that the turnover of I^{131}-labeled angiotensin (AT) after a single intravenous injection

of this substance was abnormally slow in essential hypertension.[27] This occurred despite the fact that in vitro the serum of hypertensive subjects degraded AT more rapidly than did the serum of normotensive subjects.[28] What is more, when a nonvasoconstrictive analogue identical in structure to AT except for one amide in place of an amine group was labeled with I^{131} and injected into hypertensive and normotensive subjects, there was no difference in turnover between the two groups.[29] Thus the slow turnover of AT was clearly related to its vasoconstrictive properties.

Yet when tritium-labeled NE was injected for 2 minutes or infused for 30 minutes into normotensive and hypertensive subjects, no difference in short-term turnover could be demonstrated. Nor was there any difference in the rate of production of metabolites.[4] When long-term turnover after infusion was analyzed, however, presumably representing the material released from the stored pool, there was a difference between the hypertensive and the normotensive groups (shorter disappearance time).[30]

It must be remembered that long-term disappearance of AT from the blood may either be dependent on a larger pool size or may be a first-order reaction,[27] that is, a certain percentage of the total pool disappears per unit time, regardless of the size of the pool. Carrier AT has been shown to have no effect on the disappearance slope, but it may be difficult to alter pool size with carrier highly active physiologically. The decrease in the AT disappearance slope in hypertension may therefore indicate that it enters the NE storage pool and is affected by corresponding pool dynamics. Carrier NE has been shown to have no effect on the NE disappearance curve during the second to fourth hour after labeling of the pool, but whether it affects the zero to second or fourth to sixteenth hour portions of the curve has not as yet been ascertained.[24, 30] In any case, although the change in the fourth to sixteenth hour NE disappearance slope in hypertension might conceivably be attributable to a defect in the vascular smooth muscle receptor, it is more likely that this too represents a defect in NE pool dynamics in the disease.

Let us examine this possibility more closely. Recent studies have shown that nerve cells probably synthesize effector substances continuously and store them.[31] Electrical impulses serve only to release the effector substance from the store, which embodies not only the effector substance but the storage mechanism as well.[8] If the release of NE were normal in hypertension but pool dynamics were changed, what could be affected chiefly might be the size of the fixed pool or store, which could be small.

Would such a situation fit the experimental facts? It would in great part. Increased vascular reactivity, at least initially, could be explained by the availability of more free NE, since less would be accepted by the small neurovascular stores. These decreased NE stores might involve a defect in the NE storage mechanism. The changed turnover of labeled NE in hypertension could be explained by a different degree of dilution or rate of release of the label because of altered NE pool dynamics. The facts with reference to AT and other vasoactive substances would also be explained, provided that it was postulated that these substances entered the same storage pool, presumably in sympathetic nerves and chromaffin tissue in general, as does NE. The vessels would thus be more reactive to AT as well as to NE for similar reasons. The slow turnover of the peptide in hypertension might also be explained on the basis of altered dynamics within the storage pool. Indirect evidence for such an effect is the demonstration by McCubbin and Page[33] that tyramine, which releases stored vasoactive substances, produces a greater rise in blood pressure after prior infusion with AT than after prior infusion with NE.

How does the sodium ion interrelate with this complex? Dahl[34] has shown that the sodium pool in essential hypertension is increased. It seems to us that this can best be related to the function of smooth muscle. There is evidence that whenever smooth muscle contracts more than is normal, it tends to accumulate sodium,[35] and as it hypertrophies it accumulates more sodium in proportion to the increased volume of vascular tissue, as well as because of increased concentration. Whether this accu

mulation of sodium also involves imbalances between nerve pool and smooth muscle pools is unknown at present. It is this accumulation of sodium in the walls of *the blood vessels in the renal medulla that* seems to explain best the increased natriuresis on salt loading in the patient with essential hypertension. Another cause for the accumulation of sodium in vessel walls is stimulation of the secretion of mineralocorticoids from the adrenal cortex. These substances not only favor renal retention of electrolytes but also may have a direct effect on the tissues in terms of shift of ions into or out of smooth muscle cells. It is curious that aldosterone causes more renal retention of sodium in normotensive subjects than in patients with essential hypertension, perhaps because on salt loading the tendency for the hypertensive patient to excrete salt balances the salt retaining effect of the aldosterone. On the other hand, aldosterone produces more increase in vascular reactivity in the hypertensive group, which suggests a direct effect on tissues. It is apparent from experiences with primary aldosteronism, however, that the sodium factor alone is capable of increasing reactivity in a normotensive subject to the point at which hypertension as such is produced. On the other hand, glucocorticosteroids have little effect on the retention of sodium by the kidney yet increase responsiveness of blood vessels in normotensive subjects only and not in hypertensive patients. This suggests perhaps that these substances act by decreasing the stored pool of NE in chromaffin tissue including that of sympathetic nerves. These steroids would thus have little effect on the hypertensive patient because in him this pool is already small.

In regard to tissue sodium concentrations, it is our view that an optimum zone exists in blood vessels for modulation of contraction. If concentrations are increased or decreased above or below this zone, respectively, responsiveness of blood vessels increases. Thus sodium depletion by natriuretics increases reactivity in the normotensive group and decreases it in the hypertensive group,* whereas aldosterone increases reactivity especially in the hypertensive patients and to a lesser extent in normotensive subjects. We see, therefore, that in addition to small NE pool size there may be a second factor which increases the responsiveness of blood vessels in hypertension, namely, accumulation of sodium. This effect will be much more pronounced, however, in the hypertensive patient with his small NE storage pool than in the normotensive subject or, for that matter, in the patient with pure renal hypertension. The latter has been shown to have normal or only slightly increased reactivity to NE. There are other reasons for the hypertension in such patients, however, including hypervolemia and increased cardiac output as in acute glomerulonephritis and edema of blood vessels walls followed by intimal proliferation and arteriolosclerosis initiated by increased vascular sodium concentration. If renal disease complicates essential hypertension, however, not only will these structural factors be brought into play, but also because the optimum zone of sodium concentration in such patients is easily exceeded, the already increased vascular reactivity to vasoactive substances may be expected to be augmented still further.

Most recent doctrine indicates that, whereas adrenocorticotropic hormone (ACTH) is the chief stimulant of glucocorticosteroid secretion, AT is probably the major stimulant for the secretion of aldosterone. What then can we say about the relationship of the kidney to hypertension, a most thorny and difficult problem? The view held at one time to the effect that human hypertension is caused by the increased secretion of renin, which is converted into AT, and produces direct vasoconstriction, is probably incorrect. It can be shown from studies on blood level and turnover that the amount of AT present in the body, even in patients with hypertension, is insufficient to produce vasoconstriction despite increased reactivity in the hypertensive patient and despite the possibility of the existence of a levo-rotatory form of AT which is more

*For footnote see opposite column.

The effect may be different, however, in different vascular regions. Feigal and associates have demonstrated a decrease in vascular responsiveness in striated muscle of normotensive ... after the administration of chlorothiazide.

potent than the racemic form ordinarily available. The immense discrepancies between blood pressures and AT levels in hypertension and in congestive heart failure would remain unexplained. Also early in the course of hypertension, the vessels after inhibition of neurogenic vasoconstriction are not intrinsically narrowed as they would be if a vasoconstrictive substance were circulating.[63] Moreover, how could one expect the blood pressure to be effectively decreased by drugs which influence the sympathetic nervous system if circulating AT were producing the vasoconstriction?

On the other hand, when sensitive methods are used, even though not enough AT is present to produce increased vasoconstriction, it can be demonstrated that more AT is in the body of the patient with hypertension than in that of the normotensive subject.[4] We believed that originally some of this difference was attributable to a slow degradation of AT, but if it enters the NE stored pool and is affected by dynamics within the pool, this too could satisfactorily account for the slow turnover. No matter what the mechanism, however, the chief effect of the increased AT would be to increase the production of aldosterone which, together with the direct effect of AT on the kidney, would influence the concentration of sodium in the walls of the blood vessels.[64, 65]

In renovascular hypertension, however, enough AT can be demonstrated in arterial blood to be responsible for some direct vasoconstriction.[64, 6] Yet it is likely that even here the blood vessels are affected to a greater extent secondarily, directly via an effect on the kidney as well as indirectly via increased mineralocorticoid production with an additional effect on sodium metabolism and therefore on vascular responsiveness. Otherwise how could one explain the response of such patients to antihypertensive drugs?[66]

Regardless of the fact that the production of AT is insufficient to account for the vasoconstriction of hypertension, the increased amount present in hypertension seems to call forth increased production of the degrading enzyme in the blood, so that the in vitro degradation of AT is greater in hypertensive than in normotensive subjects.[5, 67] Moreover, there is some evidence that there is a heat labile inhibitor of this reaction,[5] but this is not agreed upon by all workers.[6] The degrading enzyme moves electrophoretically with the serum globulins, whereas the heat labile inhibitor seems to move with the serum albumin.[68]

Let us now try to visualize what must happen in essential hypertension develops in an individual person. This person is born with a defective gene which produces a defect in the system responsible for chemical changes in sympathetic nerves and probably in chromaffin tissue in general. This in turn determines the size of the NE storage pool, of which adenosine triphosphate has been identified as an integral part. The net result is a smaller than normal store of NE. However, release and catabolism of NE is probably quite normal.

As NE is released by nerve impulses, some of it stimulates smooth muscle and some goes back into the stored pool. Since this stored pool is small, however, less goes back into the pool and more free NE is available for vasoconstriction. But because of the chemical modulations involved, excessive free NE, and hence vasoconstriction, will be produced only under conditions of stress. Thus the normal individual will have comparatively little free NE available in a stressful situation, whereas the hypertensive subject will have more.[69] Determinations of catecholamines in the urine or blood will therefore not be different in the two groups initially, except under conditions of stress, which are presumably manifested in both groups by increased sympathetic nerve firing. The same process operating on catecholamine content of the heart, especially in this initial stage of essential hypertension, will make it beat more forcefully and faster, producing a measurable increase in cardiac output.[70]

Why then could we not attribute the entire difference in this stage of the disease to psychic factors, that is, more sympathetic nerve discharge in the hypertensive than in the normotensive subject? We could, except that it would leave unexplained the normal urinary catecholamines and the changed turnover of NE or AT

in the hypertensive patient. These can all best be explained by postulating relatively normal NE release but a decrease in the rate of storage of NE, as already indicated. One may at this point ask how the patient *with postural hypotension or the one* who has undergone sympathectomy differs from the hypertensive subject. Both have small NE *storage pools, the hypotensive subject* on a structural basis. Both, therefore, demonstrate increased vascular responsive*ness to infused NE.*[11] Both have decreased NE storage, although there may be a tendency for the intact sympathetic structures in the postural hypotensive or sympathectomized patient to compensate for the loss of catecholamine producing tissue.[72] The major difference is that in the hypotensive patient there is decreased release of NE because nerve firing is made impossible by the structural impairment. This is manifested by low levels of both catecholamines[72] and VMA[73] in the urine.

To return now to the hypertensive subject, however, he will, as time goes on, [illegible] a net increase in vasoconstriction over the normotensive, and for this reason sodium will begin to accumulate in the walls of his blood vessels. Excessive ingestion of salt[74] either is the result of salt *hunger so produced in part, or is habitual* and hastens the process in the blood vessels. Gradually the point is reached at which the *optimum zone* of sodium concentration in the vessel wall is exceeded and the vessel begins to become more responsive to NE even when produced normally and certainly when produced in excess during stressful situations. This accumulation of sodium in the walls of the renal blood vessels makes the hypertensive patient lose more salt on loading (countercurrent theory)[5, 6, 75] and contributes to salt hunger. Meanwhile sodium also accumulates in the walls of the carotid sinus and other vasosensitive areas, rendering them less sensitive to elevations of pressure and resetting their activity at a higher level of blood pressure.[75, 5] The effect of sodium on *edema of* blood vessel walls as an additional factor has already been discussed.

The *renin produced* by the juxtaglomerular cells of the kidney continues to act on angiotensinogen to produce AT. In fact, the hypertensive patient may exhibit some increase in the production of renin because of constriction of small vessels and renal ischemia,[76] but whether there is increased production of AT in essential hypertension *has not yet been* ascertained. The AT enters the NE stored pool, is influenced by altered NE pool dynamics, and may *tend to accumulate in the body. The AT* acts directly on the kidney but also stimulates the production of mineralocorticoids by the *zona glomerulosa* of the adrenal cortex. These mineralocorticoids counteract the salt-losing tendency of the kidney but produce an increase in the sodium content of the walls of the blood vessel, probably more by direct action on tissue ion shifts than by their action on the kidney.

What is happening to the structure of the blood vessels while all this is going on? There is some edema initially and, because of increased vasoconstrictive work, hypertrophy of smooth muscle. Eventually injury to the intima is produced, and there is some intimal proliferation and, finally, in some vessels, necrosis of the vessel wall and thrombosis. This process produces an anatomic increase in vascular resistance and is less reversible than the prior changes.[11, 12]

Let us now ask what is meant by autoregulation and how this fits in with the events in the evolution of essential hypertension? It has been *known for many* years that when blood pressure is decreased, especially to the point of ischemia, capillary dilatation takes place, presumably because of the accumulation of metabolites, some of which produce reactions like histamine.[11, 15] This process is known as reactive hyperemia and is believed to be independent of the function of the sympathetic nerves. The chief structures involved are the precapillary arteriolar sphincters[16] rather than arterioles of branching orders proximal to the sphincters. *Peptides such as bradykinin* also play a role in the process, as Burch and DePasquale[17] have recently demonstrated.

In addition, however, it has been shown that in most vascular beds elevation of the perfusing arterial pressure produces an opposite reaction on the part of the precapillary sphincters, consisting of constriction of those structures.[11, 33] This part

of the process has been less completely studied than reactive hyperemia and is still disputed [90,91] In fact the mechanisms which determine such reactions are unknown Nevertheless it appears that even after denervation flow is proportional to pressure within a zone which is broad in some vascular beds and narrow in others whereas above or below this zone the precapillary sphincters react by tending to keep blood flow normal This process is pronounced in the kidneys possibly because in the glomeruli and nowhere else in the body capillaries are interposed between two arterioles There may be other explanations as yet unknown for this peculiar renal sensitivity to changes in perfusing pressure

As a result however the kidney is the first organ to exhibit the effects of hypertension and because of chronic ischemia there is a striking loss of kidney substance as hypertension runs its course in time [97] Autoregulation is probably one factor and possibly the most important one which influences this loss of tissue It is not known however exactly how much influence the ischemia has on the renin angiotensin system except when there is narrowing of the main renal artery In such cases it appears that there may be a measureable stimulation of renin and AT production [64,86]

If the treatment of hypertension is viewed in the context of all the preceding discussion it becomes more intelligible Although drug therapy has developed empirically it is really aimed at the major physiologic abnormalities in the disease Decreasing the sodium content of vessel walls decreases vascular reactivity to NE in patients with essential hypertension Edema of blood vessel walls however is also decreased Today the most effective drugs employed for this purpose are chlorothiazide and its congeners [98,9] and aldosterone inhibitors such as spironolactones [86] These substances act primarily on the kidney but may affect the tissues as well Decreasing the availability of free NE also decreases vasoconstriction This can be accomplished in several ways Blockade of the nervous system at various levels can reduce firing [97,11] competitive inhibition may occur at the nerve endings [9,100,101] and other drugs may deplete NE stores or favor storage over release of free NE [10,102] These mechanisms are still imperfectly understood It should also be emphasized that the mode of action of the drug hydralazine is also not yet clear [104]

The question may now be asked as to why after cessation of treatment blood pressure does not immediately rise to its original level This may not be merely a matter of a resetting of the barostats [115] It may take time for the stores and turnover of NE to return to pretreatment levels It also takes time for the sodium content of the walls of the blood vessels to increase and for increased vasoconstriction to produce structural changes in the vessels again If meanwhile the stress factors in the life of the individual have decreased all these will play a role in keeping the blood pressure from rising to its prior level although it may eventually do so

We may now examine the relationship of hypertension to such conditions as arteriosclerosis renal disease and diabetes mellitus There are four types of arteriosclerosis [106,105] (1) atherosclerosis (2) Monckeberg s arteriosclerosis (3) arteriolosclerosis and (4) thromboatherosclerosis The only type directly related to hypertension is arteriolosclerosis [109] Any type of hypertension regardless of its mechanism is capable of producing arteriolosclerosis [82,110,111] It is classically seen in the course of the development of essential hypertension especially as it goes into the accelerated phase It may be considered to be a result of vasoconstriction in hypertension as well as a potentiating cause Arteriolosclerosis can however exist in the absence of hypertension A patchy type is seen in diabetes mellitus [114] Arteriolosclerosis may be found as a residue of treated hypertension or of hypertensive disease modified by a coronary occlusion or a stroke [115] It is also likely that such sclerosis occurs as a consequence of aging independent of hypertension and the other diseases mentioned [116]

All other types of arteriosclerosis occur independently of hypertension This applies particularly to Mönckeberg s sclerosis which is a calcification of the media of medium sized arteries and may be caused by ischemia of these regions of the arterial walls [117] This is a relatively benign

dition usually independent of hypertension although it can apparently be accelerated by hypertension under certain circumstances

On the other hand atherosclerosis[1,5] and thromboatherosclerosis are definitely accelerated by hypertension although these conditions are clearly also dependent on such factors as fat and cholesterol metabolism[119,120] and on *hydraulic forces*[3,4,17] as well as on local stresses produced by constrictions of neurogenic origin[3] This kind of arteriosclerosis involves particularly the aorta and arteries up to and including the fourth branching order Arteries beyond this are more a part of the arteriolosclerotic process although the dividing line between the two cannot be clearly demarcated

There is a type of periarteritis nodosa associated with severe hypertension and renal impairment[1,3,4,5] but not characterized by either fever eosinophilia or rapid sedimentation rate which is indistinguishable clinically from malignant hypertension This type of periarteritis thus becomes a pathologic diagnosis only and it seems questionable whether cases of this kind should be classified in this way despite involvement of the entire arteriolar or arterial wall

The influence of the hypertensive process on the kidneys has already been discussed Aside from the adventitious coexistence of essential hypertension with renal disease[1,3] such as pyelonephritis glomerulonephritis and diabetic glomerulosclerosis it seems likely that the presence of hypertensive nephrosclerosis predisposes to the development of some renal diseases particularly pyelonephritis[1,4,17] One must now ask what the influence of renal disease as such is on the hypertensive process regardless of whether the renal disease is a complication of the hypertension or part of an additional process

In acute glomerulonephritis it seems quite clear that hypertension when it occurs is produced by retention of sodium chloride and water by the kidney with resultant hypervolemia and increase in cardiac output[127] Chronic renal disease however may be quite severe and be unassociated with any hypertension[128,129] This is seen particularly in the nephrotic syndrome but may be observed also not infrequently in chronic renal failure

It is a mistake however to equate hypertension with peripheral systemic vasoconstriction or vascular narrowing without knowing whether the cardiac output is increased or decreased Anemia if severe may also influence the situation by decreasing viscosity[130,131] and the same may be said for *hypoproteinemia*[132] Also the effect of edema on the entire complex of vascular reactivity—for example on the amount of sodium in the walls of the blood vessels or on its partition between tissues and blood vessels or on the partition of free and stored NE—is unknown These remarks apply also to congestive heart failure Renal disease influences electrolyte metabolism directly[30,31,133,134] however and also indirectly via the angiotensin aldosterone mechanism[61,77] On the other hand it is doubtful with the possible exception of the Goldblatt kidney[135] that renal disease produces enough AT to increase the blood pressure directly to a significant extent[61,6] The exact interrelationships here are complex and will yield their secrets only to prolonged investigation

The relationship between hypertension and diabetes mellitus is even more obscure That one exists is attested to by the increased incidence of hypertensive vascular disease in diabetic patients[136,137] Is this attributable to the sclerosis of small blood vessels which is known to occur early in the course of diabetes[138] or is it attributable to diabetic glomerulosclerosis despite the fact that this usually results in a nephrotic syndrome when severe[2,139] But if so what are the mechanisms involved? One may also ask of course whether the abnormality in glucose metabolism influences the blood vessels directly influences the balance between free and stored NE or has no effect on blood vessels at all Also is steroid metabolism involved in the vascular process[2,140] Again no satisfactory answers to these questions are available and only future research will provide them

Summary and conclusion

Essential hypertension is a hereditary disease that is probably transmitted by an abnormal gene which modifies catecholamine metabolism It is characterized by

increased vascular reactivity to vasoactive substances The evidence available today suggests that the cause for this may be a decrease in the size of the pool of stored l norepinephrine (NF) despite relatively normal release of this substance by nerve impulses except under conditions of stress

Increased vasoconstriction produces a concomitant increase in the concentration of sodium in the walls of the blood vessels Beside the effect of this in resetting baro stats and in producing edema of the vessel walls it also makes the vessel more re active to vasoactive substances especially in the subject with essential hypertension

Angiotensin II (AT) is produced in in sufficient amounts to account for any direct vasoconstriction except perhaps in Goldblatt hypertension and even here the effect is partial The major actions of AT therefore are direct effects on the kidney and stimulation of the production of aldosterone Aldosterone has a direct action on blood vessels especially in the hyper tensive subject as well as an effect on the kidney s handling of electrolytes The in creased amounts of AT in the body of hypertensive patients may be caused by a decrease in its clearance from its somewhat larger than normal storage pool The inter relationship of the AT and NF pools affects in turn AT metabolism by virtue of al tered NE pool dynamics The AT does however stimulate an increase in serum an giotensinase in essential hypertension

Therapy becomes intelligible in this context and is aimed at decreasing the con tent of sodium as well as of free NF in blood vessels

The interrelationships between hyper tension and autoregulation arteriosclerosis renal disease and diabetes mellitus are discussed

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Fundamentals of clinical cardiology

Paradoxical splitting of the second heart sound

An informative clinical notation

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Potain[1] in 1866 observed that the second heart sound (S_2) was not pure but split into two components during phasic respiration. As so frequently happens, this valuable observation lay dormant for many years until first objectively demonstrated by Katz[2] and later popularized and emphasized by Leatham[3,4] and others. With the development of cardiac diagnostic studies the hemodynamic explanation of the phenomenon has been clarified. It is now well recognized that normally the first component of S_2 is due to closure of the aortic valve and the second is due to closure of the pulmonary valve.

In the past several years numerous publications have appeared concerning normal and abnormal splitting of the second heart sound.[4-11] The majority has been concerned with the phenomenon of abnormal *persistent* splitting of S_2 and has stressed the importance of this finding. We have recently become aware of how frequently abnormal (*paradoxical*) splitting of the second heart sound is encountered. In this paper we will review briefly the general topic of normal and abnormal splitting of S_2, contrast abnormal persistent with paradoxical splitting, and propose a simple logical classification which is applicable to both types. Our main purpose, however, is to outline the circumstances in which paradoxical splitting is found. As will be discussed, when paradoxical splitting is present without obvious cause, important information is obtained which can help clarify difficult diagnostic problems.

Normal "physiologic" splitting

Splitting of the second heart sound into two distinct components occurs whenever there is asynchronous closure of the aortic and pulmonary valves. Although certain facets of the explanations cited are less well established than others, the following concept in our hands has served to best explain the clinical variations encountered. Normally, during inspiration increasing negative pressure within the thorax augments systemic venous return to the right side of the heart. Simultaneously, the capacity of the pulmonary vascular bed increases, which results in diminished pulmonary venous return to the left side of heart. This disparity of volumes imposed on the ventricular pumps during inspiration results in a prolonged period of right ventricular ejection and a (relatively) shortened period of left ventricular ejection. Thus closure of the pulmonary valve is delayed and separated from closure of the aortic valve.

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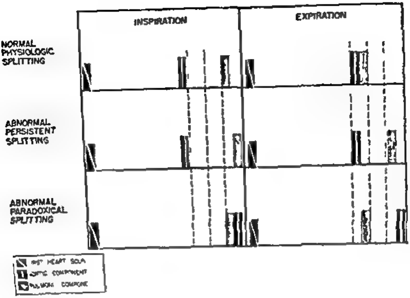

Fig 1 See text

During expiration systemic venous return decreases and pulmonary venous return increases Therefore the disparity of volumes is reversed and the closures of the aortic and pulmonary valves occur at or about the same time These hemodynamic events are readily recognized on auscultation in the pulmonary area [1] Thus the sounds of valve closure comprising S_2 are separated maximally during inspiration and minimally or not at all during expiration as shown in Fig 1 (It is to be noted that the apparent movement of A in the normal heart is exaggerated for the purpose of emphasis)

Abnormal splitting

Variation from the normal respiratory relationships of aortic and pulmonary valve closure results in abnormal splitting of S_2 It may be generalized that any circumstance that either significantly *prolongs* or *shortens* the normal ejection period of one ventricle without significantly influencing the other will change the relationship of aortic and pulmonary valve closure and abnormal splitting of S_2 will result If the period of right ventricular ejection is prolonged abnormal *persistent* splitting will occur if the period of left ventricular ejection is prolonged abnormal *paradoxical* splitting will be present We have found that the following classification (Table I) modified from Leatham [2] is useful for tabulating these circumstances It is applicable to either right or left ventricular involvement and allows the clinician a format for analyzing the findings in a particular case

It can be seen that in all situations except diminished resistance to ventricular ejection a prolonged period of ejection of the involved ventricle will result

Abnormal persistent splitting

If the period of right ventricular ejection is *prolonged* for any reason or the period of left ventricular ejection is *shortened* closure of the pulmonary valve will be relatively or absolutely delayed and separated from closure of the aortic valve This separation will be present at all times without refer

Table I Abnormal splitting of S_2

- I Electrical causes
- II Hemodynamic causes
  - A Volume loads
    - 1 Recirculation shunts
    - 2 Semilunar valve insufficiency
  - B Pressure loads
    - 1 Outlet obstruction
    - 2 Vascular hypertension
  - C Ventricular dysfunction
  - D Diminished resistance to ventricular ejection

ence to the phases of respiration. The degree of separation, however, may be further modified by the disparities in normal respiratory volume (Fig. 1). The most common circumstances in which such abnormal persistent splitting is seen are well known and have been thoroughly discussed in numerous publications. They will be reviewed here only by tabulation (Table II) in the above classification.

Abnormal "paradoxical" splitting

Utilizing the same generalization previously presented, one may readily visualize how *paradoxical splitting can occur*. Thus any circumstance that sufficiently prolongs the period of left ventricular ejection will of necessity delay closure of the aortic valve and cause the aortic component of S_2 to follow the pulmonary component.[20] The sound of closure of the aortic valve will then occur temporally later in both phases of respiration. In such a circumstance the normal increase in volume imposed on the right ventricle during inspiration results in a delay in closure of the pulmonary valve, and the pulmonary component blends with the aortic. During expiration diminished systemic venous return allows earlier closure of the pulmonary valve, and the components of S_2 separate. Thus, in contrast to normal (Fig. 1), S_2 becomes single or nearly so with inspiration and splits into two components during expiration—reversed or paradoxical splitting.

Table II. Abnormal "persistent" splitting of S_2

I. Electrical causes
   Right bundle branch block[9,1]
II. Hemodynamic causes
   A. Right ventricular volume load
      1. Recirculation shunts (left-to-right shunts)
         a. Atrial septal defect[1,11,12]
         b. Anomalous pulmonary venous drainage[12]
         c. Ventricular septal defect[11]
      2. Pulmonary valve insufficiency[13,14]
   B. Right ventricular pressure loads
      1. Outlet obstruction[5,9]
         a. Valvular } Pulmonary stenosis
         b. Subvalvular } Pulmonary stenosis
         c. Supravalvular } Pulmonary stenosis
      2. Pulmonary hypertension—primary or secondary (narrow splitting and accentuated pulmonic component)[23,25]
   C. Ventricular dysfunction
      1. Right ventricular failure[16,17]
   D. Diminished resistance to left ventricular ejection
      1. Mitral insufficiency[18]
      2. Ventricular septal defect[11]

The clinical conditions that give rise to paradoxical splitting of S_2 can also be conveniently tabulated (Table III) in the general classification previously presented. The majority represent situations that will prolong the period of left ventricular ejection. One exception is the circumstance of paradoxical splitting of S_2 due to a shortened period of right ventricular ejection. This could be seen in isolated tricuspid insufficiency. However, this lesion must be extremely rare. The authors have not encountered it, and it is included as a theoretical (although logical) possibility.

The general categories (Table III) will be briefly reviewed and representative phonocardiograms presented.

Electrical causes of paradoxical splitting. Paradoxical splitting of S_2 was recognized shortly after Wolferth and Margolies[10] demonstrated that ventricular asynchrony accompanies complete left bundle branch block. Today this is a well-recognized clinical entity, and it is the rare patient with left bundle branch block who does not exhibit this abnormality. Indeed, Gray[19] has stated: "A recognizable delay of aortic closure with paradoxical splitting of the second heart sound may be regarded as an essential clinical feature of left bundle branch block." The frequency with which paradoxical splitting is found in left bundle branch block is strong evidence that mechanical delay *must* accompany the electrical delay and tends to refute the studies[1] which did not (experimentally) confirm ventricular asynchrony in left bundle branch block.

Paradoxical splitting of S_2 is also occasionally found in the Wolff-Parkinson-White syndrome (Fig. 2). It is most frequently present in the Type B form and suggests, as pointed out by March and associates,[20] that right ventricular depolarization and ejection occur prematurely in this form of Wolff-Parkinson-White

syndrome resulting in a relatively delayed period of aortic valve closure. The presence of paradoxical splitting in these conduction disturbances has no real clinical importance.

Hemodynamic causes of paradoxical splitting

LEFT VENTRICULAR VOLUME LOADS. The literature has emphasized the effect of right ventricular volume loads (ASD, VSD, etc.) on splitting of S_2 but minimal mention has been made of the effect of left ventricular loads. It is reasonable to assume that any condition, congenital or acquired, which significantly increases left ventricular stroke volume is likely to increase the period of left ventricular ejection and result in delayed closure of the aortic valve. The presence of paradoxical splitting may therefore provide a bedside estimate of the volume load imposed on the left ventricle. The best known example of such volume load is patent ductus arteriosus. We, like Gray,[19] have found that the presence of paradoxical splitting in patent ductus arteriosus is a reasonable clinical index that the magnitude of shunt flow is substantial. When paradoxical splitting is found in this condition, one can infer that the ductus is large and that pulmonary vascular resistance is relatively low in order to allow a significantly increased left ventricular volume load.

Aortic regurgitation is another circumstance that imposes a volume load on the left ventricle. We have found that quite frequently the aortic closure component remains audible in spite of valvular damage. Thus the severity of aortic valvular insufficiency can also be assessed by notation of S splitting. When both components of S are audible, the presence of physiologic splitting indicates a milder degree of regurgitation than is present when the splitting is paradoxical (Fig. 3).

LEFT VENTRICULAR PRESSURE LOADS. It would appear that the left ventricle can cope more efficiently with pressure loads than with volume loads. Thus significant obstruction to left ventricular outlet or increased systemic vascular resistance is frequently seen without appreciable delay in the period of left ventricular ejection.[23,25] Absence of paradoxical splitting, therefore, does not preclude a serious left ventricular pressure load. When it is present, however, in aortic stenosis (Fig. 4) or hypertension, one can state with assurance that the lesion is severe. In hypertension, paradoxical splitting has been seen only when there is significant clinical impairment in left ventricular function.

LEFT VENTRICULAR DYSFUNCTION. When paradoxical splitting is found on physical examination, the presence of typical cardiac murmurs, hypertension, or readily defined electrocardiographic abnormality makes the cause apparent. We have become aware, however, that paradoxical splitting is frequently encountered when no obvious electrical or hemodynamic cause is discernible. It is in such cases of unexplained paradoxical splitting that we have found this bedside observation to be most rewarding. In keeping with the previous discussion, it is evident that some factor must be present to sufficiently prolong left ventricular ejection and cause paradoxical splitting. It would seem reasonable that any circumstance that results in impaired left ventricular myocardial contractility may result in prolonged ejection. Such

Table III *Abnormal paradoxical splitting of S*

I. Electrical causes
   1. Left bundle branch block
   2. Wolff Parkinson White syndrome
II. Hemodynamic causes
   A. Left ventricular volume load
      1. Recirculation shunt
         a. Patent ductus arteriosus
         b. Aorto-pulmonary window
         c. Anomalous systemic venous return (personally observed and confirmed)
      2. Aortic valve insufficiency
   B. Left ventricular pressure load
      1. Outlet obstruction
         a. Valvular }
         b. Subvalvular } Aortic stenosis*
         c. Supravalvular }
      2. Vascular hypertension—systemic hypertension of any cause
   C. Left ventricular dysfunction
      1. Myocardial infarction
      2. Left ventricular failure
      3. Coronary insufficiency
   D. Diminished resistance to right ventricular ejection
      1. Tricuspid insufficiency

lesions may be inflammatory, ischemic, or necrotic left ventricular disease. We have elected to group such conditions as examples of "left ventricular dysfunction."

It is generally accepted and well publicized that right ventricular failure is accompanied by abnormal persistent splitting of S_2.[19] Less well known is the fact that left ventricular failure from any cause is usually accompanied by paradoxical splitting. In florid heart failure, however, the presence of pulmonary râles and rhonchi and the relatively muffled heart sounds make critical auscultation difficult. In such cases the problem is obvious, and the notation of paradoxical splitting would add no particularly useful information. In subtle left ventricular failure, however, this observation can be of great help in resolving a problem case and directing proper management.

We have found that paradoxical splitting after myocardial infarction is almost the rule, and we are surprised that it has not been previously noted.[24,25] The correlation has been so good that we now question the presence of acute myocardial damage if paradoxical splitting is absent. Conversely, the notation of paradoxical splitting in patients with suggestive chest pain but normal electrocardiograms has often correctly dictated appropriate treatment for acute myocardial infarction. In the usual patient with acute myocardial infarction, paradoxical splitting persists for 12 to 48 hours. It may disappear transiently during this time, but frequently the exertion of merely rolling over in bed will cause its return. We are presently studying the possible prognostic and therapeutic significance of this sign in acute myocardial infarction.[25]

Even more fruitful has been the observation that paradoxical splitting frequently accompanies episodes of angina pectoris. Wood[9] has also noted this phenomenon. This finding has often helped us to clarify the all too common clinical problem of "atypical chest pain." Currently, we are correlating the notation of S_2 splitting with electrocardiographic changes developed on exercise.[30] To date, the correlation of a positive exercise test and transition from physiologic to paradoxical splitting has been impressive.

The following brief case reports indicate some of the diverse clinical circumstances in which the notation of paradoxical splitting has proved to be helpful. They are included as examples of the value of this auscultatory observation in two basic areas: (1) the decision whether a left ventricular abnormality is actually present; (2) the conclusion whether an acute cardiopulmonary problem is basically cardiac or pulmonary.

Case reports

Case I. A 14-year-old boy was hospitalized on the Orthopedic Service with a diagnosis of septic arthritis and was acutely ill on admission. A painful, tender, and swollen right ankle and hip had been present for 1 day, accompanied by an impetiginous dermatitis of both lower extremities. Cultures after arthrotomy of the right hip were sterile. At this time paradoxical splitting of S_2 was heard and the diagnosis of rheumatic myocarditis was proposed. Twenty-four hours later his originally normal electrocardiogram showed a Wenckebach conduction defect, which promptly responded to steroids. Antistreptolysin titers during the next 6 weeks declined from 1/500 to 1/175.

Case II. A 37-year-old airman was hospitalized because of myalgia, low-grade fever, and nausea and vomiting of 3 days' duration. The early observation of a friction rub at first appeared to resolve the problem diagnostically. However, within 24 hours paradoxical splitting of S_2 was noted by the resident physician (Fig. 5). This finding was thought to indicate the presence of active myocarditis. Despite repeated observation, it was 48 hours before cardiomegaly, abnormal electrocardiogram, and prolonged Decholin circulation time developed. Venous pressure remained normal throughout his acute illness. Subsequently, the patient manifested extreme lability of the blood pressure, tachycardia, dyspnea, and mental confusion, and a viral encephalomyocarditis was diagnosed presumptively. After 5 days of serious illness, improvement was first heralded by the return of physiologic splitting of S_2. Thus far it has not been possible to establish culturally or serologically any etiological agent.

Case III. A 47-year-old officer was hospitalized because of possible myocardial infarction. Chest pain, although suggestive in character, had been unusually brief in duration. The electrocardiograms showed only elevation of the S-T segment in the right precordial leads. One determination of SGOT was elevated, but other laboratory findings were normal, and the vital signs were completely stable. Because of the presence of paradoxical splitting of S_2, myocardial infarction was considered probable and the patient was treated accordingly. During the ensuing 2 weeks, there were continuing nonspecific electrocardiographic changes, but it was 18 days before the electrocardiogram became clearly diagnostic of diaphragmatic myocardial infarction.

Case IV. A tense 43-year-old soldier was seen in consultation because of a vague chest pain. On the basis of a detailed clinical history, his complaint was

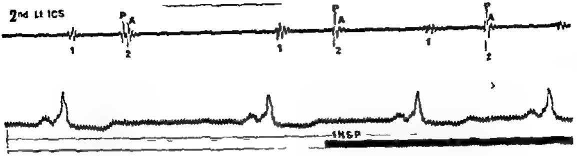

Fig 2 Paradoxical splitting of S_2 in Wolff Parkinson White syndrome (Type B) (All phonocardiograms included were recorded with a Sanborn Twin Beam Model 62 from which the upper portions of the time lines were deleted)

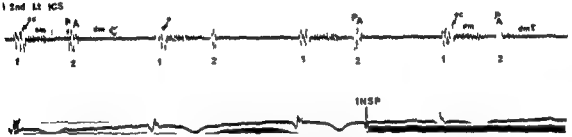

Fig 3 Paradoxical splitting of S_2 in aortic insufficiency (post traumatic) The phonocardiogram demonstrates the paradoxical relationship of the sounds of aortic (A) and pulmonary (P) valve closure An aortic ejection murmur (*sm*) is heralded by an ejection click (*ec*) There is a pandiastolic murmur (*dm*) of aortic insufficiency

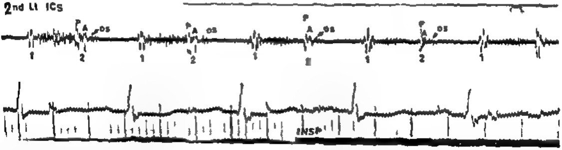

Fig 4 Paradoxical splitting in aortic stenosis (combined aortic and mitral stenosis) The paradoxical relationship of the sounds of aortic (*A*) and pulmonary (*P*) valve closure is easily seen A well defined opening snap (*OS*) is also readily identified

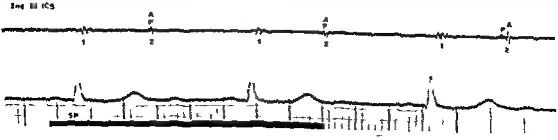

Fig 5 Paradoxical splitting in Case II

considered to be noncardiac. The resting electrocardiogram was normal, and a double Master two-step test showed only minimal junctional S-T segment depression in the left chest lead. After the exercise test the patient stated that he was exhausted, and he appeared to be hyperventilating. Approximately 5 minutes later it was noted that the heart tones were of good quality and the blood pressure was normal. There was, however, paradoxical splitting of S_2 which had not been present previously. In spite of this observation, because of the prominence of functional elements, cardiac clearance for continued duty was recommended. Approximately 3 months later the man was hospitalized with acute myocardial infarction characteristic in all regards.

Case 3. A 2?-year-old white woman with mitral stenosis, severely symptomatic, was referred for consideration of mitral valvotomy. The routine laboratory studies were normal except for a sedimentation rate of 24 mm. Mild enlargement of the left atrium was demonstrated on chest x-ray examination, and the electrocardiogram showed only minimally notched P waves. Decholin circulation time was 16 seconds. The physical findings were characteristic of significant mitral stenosis except for the presence of paradoxical splitting of S_2 after he had walked leisurely on the level. Because of this finding, the possibility of continuing subclinical rheumatic activity was considered. Surgery was postponed, and 3 months later the second heart sound exhibited physiologic splitting for the first time. Symptomatically, the patient was markedly improved.

Case 11. A 68-year-old man had abrupt onset of dyspnea with cyanosis 5 days after herniorrhaphy. Tightness in the chest was described, but it was not severe. Venous pressure was 18 cm., and the Decholin circulation time was 26 seconds. The electrocardiogram was abnormal, with S-T segment elevation and deep inversion of the T wave in the right precordial lead. The presumptive diagnosis of pulmonary embolus was questioned because of the early presence of paradoxical splitting of S_2. Deterioration continued, and death occurred 4 hours after the onset of symptoms. A careful search at postmortem examination failed to reveal pulmonary emboli or pulmonary infarction. There was, however, massive acute myocardial infarction of the anteroseptal surface of the heart.

Discussion

The notation of splitting of S_2 has particular value in that it is a *bedside* observation which does not require special equipment, undue expenditure of time, or particular talent to appreciate. As in any type of physical examination, proficiency is acquired only through diligence and practice. Thus, in examining for splitting of the second heart sound, only "attentive auscultation" can be rewarding.

Several points deserve emphasis:

1. Splitting of S_2 may not be *best* heard in the familiar "pulmonary area." Indeed, it may be inaudible in this location but well heard several centimeters distant (upper left sternal border, midsternum, or even lower left sternal border). Splitting of S_2, like gold, "is where you find it."

2. Paradoxical splitting due to left ventricular dysfunction may not be so readily appreciated as the paradoxical splitting due to other well-known causes (such as left bundle branch block). Yet, as we have indicated, it is in this circumstance that the observation is most rewarding. Often the examiner cannot distinguish two discrete components of S_2 but can readily tell that S_2 is "more pure" on inspiration and "less pure" on expiration.

3. Obviously, cardiac lesions may be combined which may be additive in prolonging ventricular ejection (i.e., ASD plus pulmonary stenosis[4]) or one may tend to "cancel" the effect of another (LBBB plus right ventricular failure).[10] We have found that the use of a classification such as the one proposed has allowed us to analyze more thoughtfully such combinations.

Summary

In recent years numerous publications have emphasized the information that can be gained by careful notation of splitting of the second heart sound. Most have dealt with abnormal *persistent* splitting of S_2, and there has been infrequent mention of abnormal *paradoxical* splitting. In this paper we have contrasted the hemodynamic bases for these differences in splitting, proposed a simple classification applicable to either type, and briefly outlined some experiences in clinical problems accompanied by paradoxical splitting. Our experience to date has indicated that notation of unexplained paradoxical splitting of S_2 may be a valuable bedside indicator of left ventricular dysfunction.

Addendum

Since this paper was submitted for publication, Yurchak and Gorlin[8] have reported their experiences with paradoxical splitting of the second heart sound in coronary heart disease. That their cases as well as ours were not documented by phonocardiography emphasizes the dif-

ficulty in recording what is readily appreciated on auscultation and further directs attention to the primary value of this finding as a *bedside* auscultatory observation

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Present status of thrombolytic therapy

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Despite the extraordinary clinical potential of thrombolytic therapy the many investigations performed with thrombolytic agents in man and the release of several thrombolytic drugs for general use many problems remain to be solved before these agents can be utilized on a practical clinical basis Only a few controlled studies have proved that blood clots can be dissolved in man and these required such complex laboratory control that the use of thrombolytic agents under any but the most elaborate research conditions is precluded

General biochemical problem Knowledge of some of the problems involved in the production and maintenance of a thrombolytic system using streptokinase (a kinase) urokinase (an activator) or glycerol plasmin requires some understanding of the activation and inhibition of the fibrinolytic process Initially streptokinase (SK) or the kinases from tissue and plasma appear to act with a proactivator to form an activator complex This complex like the naturally occurring activators in urine (urokinase) plasma or tissues then reacts catalytically with plasminogen (the proteolytic precursor) to form a proteolytic enzyme plasmin (fibrinolysin) Plasmin in turn acts upon fibrin fibrinogen and other native proteins splitting them into soluble products

The intravenously injected thrombolytic agent must be uninhibited or free in the circulating plasma to lyse blood clots Since plasma contains inhibitors to each stage of the thrombolytic system it is first necessary to neutralize these inhibitors by infusing a priming dose of the thrombolytic agent (SK or plasmin) which is equivalent to the measured amount of circulating inhibitor Only then will additional infused material result in an active thrombolytic system and clot lysis Streptokinase may be neutralized by specific antistreptokinase antibody and also by kinase inhibitor found in the alpha 2 globulin fraction of human sera Urokinase or activator may be neutralized by other inhibitors in this same fraction Plasmin (fibrinolysin) is probably neutralized by two additional inhibitors which are found primarily in the alpha 1 and alpha 2 globulin fractions

Effect of clot surface Endogenous plasminogen is adsorbed on the surface of the fibrin clot as the thrombus forms This adsorption effectively removes the plasminogen and its activator from association with and the effect of circulating natural inhibitors of both kinase and activator Thus infused SK or UK circulating free in the blood stream combines specifically with substrate plasminogen previously adsorbed on the clot and the plasmin formed on the clot as a result of this inter

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action is effectively removed from circulating plasmin inhibitor, resulting in clot lysis. In contrast to SK and UK, exogenous plasmin is not adsorbed specifically on the thrombus.

Age of clot. The freshly formed plasmin-sensitive thrombus in vivo becomes plasmin-resistant with time. This has been thought to be due to fibrin stabilizing factor, a serum factor, and endothelization. Whatever the reason, the thrombus becomes highly resistant to thrombolysis by any of the known thrombolytic agents after 72 to 96 hours.

Streptokinase (SK) and SK-containing thrombolytic agents. The enzyme streptokinase, which is contained in the streptococcal broth filtrate, was found in 1933 to destroy blood clots. Because it is a bacterial protein, preparations containing it tend to be pyrogenic. Antibody to SK may be produced in the normal individual during streptococcal infection or as a result of the parenteral injection of streptokinase. Since the amount of streptokinase antibody and inhibitor in the circulating blood varies over a hundred-fold range, the amount of enzyme required to neutralize the inhibitor and antibody must also vary accordingly. Thus the streptokinase dose requirement in man is highly variable and must be measured for each individual. One to two weeks after streptokinase therapy, the circulating antibody and inhibitor increase markedly, rendering further thrombolytic therapy impossible for several weeks or months. Unfortunately, accurate biochemical test methods for the determination of streptokinase antibody and inhibitor are both complex and time consuming; therefore, the enzyme is unsuitable for widespread clinical use.

In spite of the problems associated with SK antibody and inhibitor, 24- to 72-hour infusions of SK have been shown to be thrombolytic under well-controlled conditions. During this time numerous other biochemical tests must be run. Measurements of prothrombin, plasma fibrinogen, plasminogen, and activator are among the most important of these. The prothrombin and fibrinogen serve to warn the individual when a serious bleeding defect may occur due to hyperplasminemia; activator must be available in the circulating blood to lyse the clot, and the level of plasminogen must be maintained within very narrow limits to prevent re-formation of the clot, 2 to 5 per cent of normal; more than 2 per cent of the original level to prevent hyperplasminemia and less than 5 per cent of the original level to maintain an activator system. Since most of these tests are complicated, the fact that they must be run continually during the period of infusion has discouraged all but the most hardy investigators.

Plasmin. Plasmin is similar to SK in its interaction with inhibitors, and the amount required is also nearly equivalent to the total amount of inhibition present. Thus plasmin inhibitor must be measured and a variable priming dose of plasmin administered. However, the injection of plasmin in amounts sufficient to neutralize plasmin inhibitor also induces fibrinogenolysis and a serious bleeding defect without necessarily producing thrombolysis.

Urokinase. Highly purified urokinase (UK), which has recently become available for investigation, does not seem to be pyrogenic in man. Circulating urokinase inhibitor is a relatively weak competitive inhibitor which does not require stoichiometric neutralization, and the amounts normally present in man vary over less than a twofold range. Therefore, the priming dose of UK is relatively fixed, and preliminary measurements of UK inhibitor are not required. The level of endogenous plasminogen is not so critical with infusions of urokinase, although the exact limits have not yet been determined. In short, preliminary thrombolytic experiments with UK appear to be promising.

Conclusions. There are many problems to be solved in therapy with thrombolytic agents. It is important to recognize that even after a particular agent has, in fact, been shown to be thrombolytic under the best controlled laboratory conditions, the same agent must be re-evaluated for its clinical efficacy using simple laboratory tests for the control of routine therapy under practical conditions. Only at this time will it be possible to *begin* to determine the true clinical usefulness of thrombolytic therapy with appropriate, well-designed clinical trials.

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Pericarditis due to infectious mononucleosis*

Involvement of the heart in infectious mononucleosis is not surprising in view of the ubiquitous distribution of histologic lesions. Moreover, this occurrence is generally acknowledged with the realization that electrocardiographic aberration may be noted during the course of the disease. Conceded also is the possibility that myocardial involvement may attain clinical significance. However, the development of acute pericarditis as a result of infectious mononucleosis is not so well known nor is it often considered in the differential diagnosis of idiopathic pericarditis.

Since 1946, when Evans and Graybiel[1] presented 4 case reports to which they appended a fifth from another source, the literature has contained an occasional reference to the occurrence of acute pericarditis as a complication of infectious mononucleosis.[2-8] The cases of approximately 20 patients have been reported. As one would expect, most patients have been below the age of 30, being concentrated in the 20-29 year category. With rare exception, the patients have been male. The relationship between the onset of signs and symptoms of pericarditis and the onset of other indications of infectious mononucleosis is variable. Worth noting is the occasional appearance of what seems to be idiopathic pericarditis followed in several days or a week by the clinical syndrome of infectious mononucleosis. As is true of pericarditis in general, the symptomatology varies considerably. There are no characteristic features unique to pericarditis due to infectious mononucleosis; however, several observers have been impressed by the severity of pain experienced by their patients.

In only about one half of the reported cases has a pericardial friction rub been noted, often evanescent in character. However, electrocardiographic abnormalities have been the rule. RST segment and T wave changes of the type found in pericarditis often disappear within a few weeks but may persist for several months, particularly in the case of the T waves. In a few of the patients minimal asymptomatic transitory cardiomegaly has been described. In one report, tamponade which required pericardiocentesis was present in 3 patients and constrictive pericarditis which required surgical intervention occurred in one of these.[7] No fatalities have been ascribed to pericarditis due to infectious mononucleosis, although congestive heart failure due to concurrent myocardial involvement has been described. Histologic evidence of pericardial involvement has been limited to patients in whom death was due to happenstance or to a complication of infectious mononucleosis other than cardiac.[9-11] Although minimal lymphocytic infiltration has been noted, no instance of significant pericarditis has been reported.

Treatment of the pericarditis when it appears in the course of infectious mononucleosis is identical to that for pericarditis of any type. The need for pericardiocentesis is rare, and a satisfactory outcome is to be expected in most patients. The possibility of the development of late constrictive phenomena must be kept in mind. In seriously ill patients, corticosteroids may be as beneficial as they have been for other serious complications of infectious mononucleosis.

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Thyroxine analogues as hypocholesterolemic agents

Ten years ago it was found that the serum cholesterol could be lowered by alteration in the dietary fats.[1,2] Since then efforts have been made to find an agent which was effective in lowering the blood cholesterol yet was safe and convenient. The discovery of such an agent is an urgent problem, for until one is found there can be no answer to the question whether reduction of cholesterol is of any benefit to the patient with coronary artery disease.

Since 1922 it has been known that hypothyroidism is associated with a raised blood cholesterol and that in hyperthyroidism the cholesterol is often low.[3] But there is no direct correlation between the basal metabolic rate (BMR) and the level of cholesterol.[4,5] It was then logical to try to lower the blood cholesterol with thyroid extract. On small doses of thyroid the cholesterol-depressing effect was soon lost, but on larger doses a sustained reduction in blood cholesterol could be obtained.[7] In order to do this 325 mg. per day of desiccated thyroid was required, but on this dose there was a loss of weight and increased pulse rate.[8] L-thyroxine at a dose of 0.4 mg. per day for 3 months was given to 50 patients with a nontoxic goiter.[9] The blood cholesterol was reduced, but there was also a fall in the body weight and a rise in the BMR. Such treatment is likely to be hazardous in patients with coronary artery disease.

Many analogues of thyroxine were investigated in order to discover one in which the effect on the BMR was dissociated from the effect on cholesterol metabolism. Among those studied were L-triiodothyronine,[9,10] D-triiodothyronine,[11] D-diiodothyronine,[12] tetraiodothyroacetic acid,[13] triiodothyroacetic acid,[13,14] triiodothyropropionic acid,[17] and tetraiodothyroformic acid.[13,15] With all of these drugs the disadvantage was either a rise in the BMR or a loss of the cholesterol-lowering effect after a short interval.

The most useful analogue tested was the dextro isomer of thyroxine. This will lower the serum cholesterol in a dose which does not raise the BMR.[8,18] Pure D-thyroxine was difficult to prepare, but with recent preparations it has been found that contamination with L-thyroxine was insignificant.[8,19] D-thyroxine differed from the levo form in its more rapid removal from the blood stream and its greater concentration in the liver.[21,22] This has been suggested as the cause of the greater effect of D-thyroxine on the blood cholesterol than on the metabolic rate. It is believed to act by increasing the rate of catabolism or excretion of cholesterol, thus lowering the blood level.[23,7] D-thyroxine has been used successfully in patients with angina and hypothyroidism[8] and subsequently in reducing the cholesterol in euthyroid patients with coronary artery disease.[7] Reports of the use of D-thyroxine over short periods showed that it reduced the cholesterol by approximately 20 per cent without evidence of hyperthyroidism.[8,23,7,24] This effect on the cholesterol was achieved by gradually increasing the dose to a total of 8 to 10 mg. per day.[7] At this level some patients complained of increasing angina and were unable to tolerate the drug,[8,23] whereas others, although having no increase in the symptoms, felt better after stopping D-thyroxine.[7] Further increase in D-thyroxine to 12 to 15 mg. per day gave rise to a hyperthyroid state in some patients. The therapeutic and toxic doses of the D-thyroxine were narrowly separated.

Long-term trials have revealed that there are fluctuations in the effect of D-thyroxine on the blood cholesterol.[25] After 6 months of treatment there was an escape from the effect of D-thyroxine in a number of patients,[7,10] but this effect has not been adequately explained. A seasonal variation in cholesterol has also been found, with higher levels in the winter than in the summer.[10] This may be due to greater metabolic requirements of thyroxine by the body or increased endogenous biosynthesis of cholesterol in the winter. In normal control subjects the cholesterol does not show a seasonal variation;[25] however, a small rise in the cholesterol of less than 50 mg. per 100 ml. during the winter months has been described in convicts but not in their warders.[25,26] Administration of exogenous thyroxine over long periods may suppress the secretion of pituitary thyroid-stimulating hormone, and with greater requirements due to environmental factors during the winter a relative deficiency of thyroxine could occur, with a rise in the blood cholesterol and body weight. It is of interest that there is a seasonal incidence of myocardial infarction in young adults; 60 per cent of the cases occur between November and March.[27]

In conclusion, the early hopes that D-thyroxine would fulfill the requirements of a drug which would consistently depress the cholesterol without toxic effects have not been realized. It may be of value in some patients with hypercholesterolemia, but is

unlikely to be of benefit to patients with coronary artery disease

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Rheomacrodex in peripheral ischemia

In patients with peripheral ischemia due to arterial obstruction several factors combine to make blood flow more sluggish and oxygenation of the part less satisfactory. In addition to the limited quantity of blood and low pressure the viscosity of capillary blood may be much increased. In a lucid Short *Introduction to Hemorheology* Gelin[1] points out that the viscosity of blood increases at low rates of flow. The viscosity is dependent among other factors on red cell aggregation or sludging and the hematocrit. Low molecular weight dextran (Rheomacrodex) with a mean molecular weight of 40 000 (range 20 000 to 90 000) has been found to reduce this sludging of erythrocytes and in addition it acts as a plasma expander and reduces the hematocrit.[1,2] This results in a marked decrease in viscosity of capillary blood and a consequently increased flow of capillary blood.

Because of this property Rheomacrodex has been used as a *treatment for peripheral ischemia* by Bergentz and associates[3] and more recently by Ratliff[4] and by Fowley.[5] Bergentz and associates in their paper discuss the use of Rheomacrodex in surgery succinctly describing the indications for its use to improve the perfusion of the tissues with red cells when this perfusion is impaired by rheological disturbances. They mention its use in 2 cases of arterial embolism and 8 cases of arterial obstruction with incipient gangrene. All the patients except one were saved from amputation but no case reports or details are given.

Ratliff outlines the case of a patient who with *multiple injuries and a foot with circulation so poor* that amputation was being planned made a dramatic recovery after infusion with Rheomacrodex.

Powley describes 5 patients in whom the supply of blood to a limb or digit was seriously impaired and gangrene was present or impending who were treated with infusions of Rheomacrodex with marked improvement in the circulation and relief of ischemic pain. He mentions that it was used in other patients always with some improvement and with no complication. Although the causes of the poor flow of blood differed in these 5 cases and included thrombosis embolus traumatic occlusion of arteries *and Raynaud's phenomenon* the effect of increased capillary circulation was noted in all patients.

It is presumed with good reason that the pathology produced by fat embolism is due to obstruction to capillary blood flow. Bergentz and associates mention the use of Rheomacrodex in 7 cases of fat embolism and Seeman[6] describes another case with good result. The favorable effect is ascribed to the *improvement in blood flow in the capillaries which remain open in the part affected by the multiple minute emboli.*

Experimental evidence of the effectiveness of Rheomacrodex is *produced* by several authors. Cyrus and associates found that it protected the brain of dogs from all but minor damage by infarction when given to the animal immediately before and after ligation of the middle cerebral artery. Untreated dogs a control developed extensive infarction. Plethysmographic studies in healthy subjects and also others with high blood sedimentation rates showed a considerably increased *flow of blood in the forearm during infusion* of Rheomacrodex.[9] Gelin and Ingelman[1] showed that blood flow in the capillaries of the conjunctivae was improved when Rheomacrodex was given by infusion to patients with conditions which had led to poor capillary flow.

No side effects have been recorded—there is no effect on blood typing,[10] no effect on hemostasis in recommended dosage (but this may be changed in high concentration[11]) and no effect on biochemistry. No systemic reaction has so far been reported. Since it is a plasma expander its use in patients with pulmonary edema would not be without risk and if *the substance leaks out of the wall of the vein* there is the very brisk onset of considerable local edema.[5] The main limitation to its use is that it must be given by intravenous infusion and its effects last only while it is being given and for a few hours afterward. This means that its only value in ischemic conditions is to prevent deterioration while major arterial surgery is being planned or to tide the patient over a crisis until the collateral circulation improves or infection is overcome. Bergentz and associates and Bellman and Lölstrom[12] point out its value in maintaining adequate blood flow in the critical early stages after reconstructive arterial surgery.

It is seen that clinical reports confirm the effectiveness of Rheomacrodex as a substance with the

property of increasing capillary blood flow. As yet these reports are brief and do not deal with large numbers of patients. The use of objective means to measure the apparent increase in blood flow in ischemic limbs achieved by the use of Rheomacrodex has not yet been reported. Reports are awaited with interest, because it is apparent that it may have a valuable, although limited, place in the treatment of ischemia. It has far more to recommend it than do the vasodilators which have such a vogue at the moment.

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Fibrinolytic bleeding and its control

Excessive plasma proteolysis can induce an acute or chronic coagulation disorder and may, especially if its onset is sudden, underlie the development of a severe hemorrhagic diathesis. Such pathologic states, usually referred to as fibrinolytic disorders, complicate a variety of disease entities or major operative procedures, especially those involving cardiac bypass. Although the blood of patients suffering from this disorder frequently demonstrates multiple coagulation defects, the most striking finding is poor and slow blood clotting even after the addition of thrombin, and the clot which forms is loose and friable. Subsequently, the clot usually undergoes spontaneous dissolution in a matter of minutes to hours, and because of the latter phenomenon, the syndrome is referred to as "pathologic fibrinolysis" or "fibrinolytic bleeding." The severity of this disorder readily can be attributed to the particularly ineffective form of hemostasis present: clotting occurs slowly, with the formation of an inadequate clot which subsequently dissolves.

The key to understanding this hemorrhagic diathesis has come from studies in several laboratories which independently demonstrated that the products of the proteolytic digestion of fibrinogen interfere with the normal conversion of fibrinogen to fibrin and that the addition of such products of proteolysis to normal blood reproduces in vitro the poor, slow, and abnormal blood clotting seen in pathologic fibrinolytic disorders.

In a series of studies[1-8] our laboratory has demonstrated that during the proteolysis of fibrinogen of fibrin by plasmin (fibrinolysin), several large fragments are released which are incapable of being further digested by the action of plasmin. One of these fragments (sedimentation constant 5.27 S, molecular weight approximately 88,000), as well as its precursors, are primarily responsible for inhibiting the interconversion of fibrinogen to fibrin. This inhibition is not on the thrombin reaction per se, rather the effect is on the subsequent step, i.e., the spontaneous polymerization of fibrin monomer, and for this reason the responsible fragment is referred to as a "polymerization inhibitor." In the presence of the polymerization inhibitor, which has sites for complexing with fibrin monomer but lacks sufficient binding sites to allow for extensive polymer formation, normal polymerization is delayed and abnormal polymers are formed. This anomaly of delayed polymerization with the ultimate formation of abnormal polymers has been termed "defective fibrin polymerization," and its

significance as the major coagulation defect underlying the *hemorrhagic diathesis seen in clinically* encountered fibrinolytic disorders has been demonstrated.

Under clinical conditions this anomaly can be *most simply tested for by studying the delay in* polymerization. In the presence of excess thrombin the thrombin time is virtually a measure of the polymerization time; as a result, prolongation of the thrombin clotting time, although lacking in specificity, has proved to be a useful screening test for the anomaly. Similarly, these breakdown products, because of their ability to delay clotting, produce a prolongation of the one-stage prothrombin time and the prothrombin time, even though less specific, also correlates well with the polymerization anomaly.

The common reaction pattern frequently found in the blood of patients with hyperplasminemia (the most common cause of these fibrinolytic disorders) includes the following: delayed clotting and abnormal appearance of the blood clot, prolonged thrombin clotting time, prolonged prothrombin time (two-stage prothrombin time usually normal), reduced fibrinogen level, moderate reduction of Factors V and VIII, reduced plasminogen (profibrinolysin) level, and increased fibrinolytic activity. *Of these, the first four abnormalities in this* hemorrhagic diathesis can be traced to the effects of fibrinogen proteolysis. The other changes represent either proteolytic effects on other susceptible clotting components or evidence for activation of plasminogen, the naturally occurring precursor of plasmin. Incidentally, the demonstration of increased *fibrinolytic activity is not necessarily a* prerequisite for the diagnosis of a fibrinolytic disorder, since the factor responsible for this latter activity may be gone from the circulation at the time the study is made. However, *their effects are* still demonstrable.[4]

The biochemical mechanisms responsible for the *pathogenesis of these fibrinolytic disorders fall* under two major headings: those whereby the state is induced by a sustained increase in plasma proteolytic activity sufficient to digest large amounts of fibrinogen and those whereby markedly enhanced clotting and fibrinolysis are simultaneously occurring in large portions of the vascular bed. In *the latter situation, which probably pertains to* the obstetrical catastrophies that follow such incidents as abruptio placentae, retained dead fetus, and amniotic fluid embolism, the rapid release of *large amounts of fibrin breakdown products rather* than those derived from fibrinogen contributes markedly to the hemorrhagic diathesis. Possibly *such a mechanism also relates to patients on pro-*longed cardiac bypass surgery.

Three mechanisms exist by which increased plasma proteolytic states can be induced in man. *First*, excessive amounts of plasminogen activator may be iatrogenically administered for therapeutic purposes or released endogenously in response to profound stimuli such as severe anoxia or shock; this temporarily overwhelms normal plasma inhibitory mechanisms sustaining free levels of plasmin in the circulation for significant periods of time. Secondly, deficiencies in inhibitory mechanisms may exist among patients with disease,[4] and the appearance of plasminogen activator in amounts ordinarily insufficient to produce significant hyperplasminemia cannot be coped with adequately under these circumstances. Finally, proteolytic *enzymes other than plasmin but capable of de-grading fibrinogen* may appear in the circulation and produce a similar state; such events have been described in the late stages of some leukemias.

Utilizing preliminary electrophoresis of plasma in acrylamide gel (designed to separate fibrinogen from fibrinogen breakdown products) followed by immunodiffusion with an antifibrinogen serum in agar, Fisher[7] recently has developed a *simple and reliable tool* to investigate serially the appearance of fibrinogen proteolysis products under various *conditions, e.g., in patients with fibrinolytic bleed-*ing due to metastatic prostatic carcinoma, in cardiac bypass surgery, and in association with infusions of plasminogen activator. Such studies are now *extending our knowledge of the conditions in which* significant fibrinogen proteolysis occurs.

Fortunately, the polymerization inhibitors formed during fibrinogen or fibrin proteolysis are spontaneously cleared from the circulation; the half life is approximately 9 hours.[3] Thus, control of the underlying mechanism responsible for their production is followed by *spontaneous recovery from* the coagulation defect. Such recovery is usually rapid, since the severity of the disorder is critically dependent on the concentration of the breakdown products in the circulation.[8]

Since a great many of the pathologic fibrinolytic disorders result from excessive or protracted plasma *plasminogen activation, it is worth noting that* EACA now can be used therapeutically to block this activation.[4,9] Epsilon aminocaproic acid is a synthetic amino acid structurally similar to lysine except that it lacks the alpha amino group of the naturally occurring lysine. Since activators pre-sumably activate plasminogen by splitting lysine *bonds in the plasminogen molecule, simple sub-*stances like lysine or EACA act as competitive inhibitors to this activation. For one reason or another, EACA has proved to be much more powerful than lysine: at concentrations approximating 15 mg. per cent (a level readily achieved in vivo either by infusion or oral administration) it can *inhibit the activity of reasonably high concentra-*tions of activator. Thus, for the first time we have a substance which, when given either orally or intravenously, effectively and rapidly prevents significant plasminogen activation in biologic fluid; this has provided us with a powerful agent for the treatment of those bleeding disorders due primarily *to excessive plasminogen activation.*

Many reports, including some of well-controlled studies, now attest to the dramatic effects of EACA *in controlling fibrinolytic bleeding* in a variety of clinical states. However, on occasion patients either have not responded to the therapy or have developed severe thrombotic disease while receiving the agent.[9] Such thrombotic events have confirmed our fears about the use of EACA in those patients in whom the increased fibrinolytic activity repre-*sents a secondary response* to an underlying thrombosing state or in whom both thrombosis and

fibrinolysis are occurring simultaneously with the thrombosing state marked by the fibrinolytic response. Under these circumstances treatment of the fibrinolytic state may well result in thrombotic complications.

Under clinical circumstances we should expect to encounter at least three forms of fibrinolytic bleeding which, other than for the usual but important supportive measures, will require different therapeutic approaches: those primarily due to plasminogen activation, for which EACA is certainly the therapeutic agent of choice; those due to the presence of circulating proteolytic enzymes other than plasmin, for which proteolytic enzyme inhibitors may prove more useful—currently studies are in progress on enzyme inhibitors derived from the pancreas and parotid glands; and finally those in which intravascular coagulation and fibrinolysis are occurring together. In this latter situation effective therapy may well require the use of an immediately effective anticoagulant like heparin alone[10] or in combination with EACA. The use of EACA alone under these circumstances would be hazardous.

Obviously the proper selection of cases for a particular therapy will require clinical judgment and careful laboratory observation. Although the pattern previously described will confirm the presence of a fibrinolytic disorder, such additional findings as accelerated thromboplastin generation, complete afibrinogenemia, severe thrombopenia and a virtual disappearance of Factors V and VIII should make one suspicious of an accompanying thrombotic state as well. However, at the present time the selection of cases for each type of therapy must still be considered as little more than empirical; nevertheless, recognition of the problem should result in the development of appropriate laboratory methods designed to make our therapeutic approach more scientific and effective.

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Letters to the Editor

The Chicago Medical School
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October 17 1963

To the Editor

H. A. Lohr and associates paper Fundamentals in Vibrocardiography Precordial Accelerography and Acceleration Ballistocardiography AMERICAN HEART JOURNAL 66 108 177 1963 *refers to some authors who strongly recommended replacing acceleration ballistocardiography with vibrocardiography*. As one of the authors referred to (Reference No. 19) I should appreciate having the opportunity to make clear that the quoted paper contains no statement suggestion or implication of any kind or degree to justify Dr Lohr's reflections. Although the principal aims of Lohr's work do not seem to be clear repeated allusions to the alleged statement (six of them printed in italics (pages 109 116 bis 119 bis 123 124 175) contribute to the impression that the primary goal of the study was to question the validity of a conclusion which to my best knowledge never was reached.

It is not within the scope of my letter to discuss Dr Lohr's conclusions based on a multiple differentiating analog computer technique.

Leslie Michael Rosa M D
Associate Professor of
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To Dr Rosa

You called my attention to an error in the numbering of our references of which I was not aware. I should have quoted No. 31 of our list instead of No. 38. In the *American Journal of Cardiology* Volume 4 1959 on pages 197 and 198 you went at length into the advantages of the precordial vibrocardiogram over the acceleration ballistocardiogram. In the summary you wrote It is concluded that the slow vibrations of the thoracic wall are due to cardiovascular forces which are closely related to those recorded in acceleration total body ballistocardiograms in the same frequency range.

I am sorry if we misunderstood your intention but the suggestion *of a possible replacement of* the ballistocardiogram with the vibrocardiogram was a sensible one. We should have investigated this possibility *in any case. In quoting* you and Dr Agress we merely acknowledged the priority of your suggestion. You would not have objected to it if our results had been positive as we should have preferred ourselves.

The conclusions at the end of each section of our paper were given in italics so as to facilitate its reading.

You have worked on vibrocardiography for a long time and so have I. I had hopes of coming into contact with you on account of this paper and it is a disappointment that you took it in bad part especially after the pleasant visit Mr van Vollenhoven paid you. You did not object at the time to our paper on the same subject which was read at the Mexico Congress so it would seem to be merely our citation which annoyed you. I assure you that no offense was intended.

Last winter I spent a delightful week at Munster at the Institute for Physiology where you stayed for a long time yourself. I gave an account of this work of ours to Prof Schutz and his staff. Prof Schutz will excuse me for inadvertently citing his paper instead of yours.

We obtained your microphone only just now as Vollenhoven's luggage had gone astray. We did not have the opportunity of testing it yet.

I did a lot of clinical work from 1950 on by means of electrocapillary transducers which I made myself having learned of their existence from Kalma who published a paper in Dutch on the subject even before Mounsey did. I failed to obtain consistent results in precordial accelerography by means of various methods. This was the reason for my asking for the help of physicists in order *to do basic research on the subject of vibrocardiography* before continuing with clinical work. Basic research is destructive to many clinical illusions. Time and again it has made me feel a fool but I have submitted to this discipline and may not shun the consequences. I quite understand your vexation though and I hope that you will bear with me for causing it.

H. A. Lohr M D

The Chicago Medical School
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2020 West Ogden Avenue
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December 19 1963

To the Editor

Dr H. A. Lohr and associates paper Fundamentals in Vibrocardiography Precordial Accelerography and Acceleration Ballistocardiography AMERICAN HEART JOURNAL 66 108 177 1963 refers to some authors who strongly recommended replacing acceleration ballistocardiography with vibrocardiography. In a later undated personal letter Dr Lohr admits that he and his associates

misunderstood the intentions of the authors referred to. Nevertheless, he expressed his opinion that basic research is destructive to many clinical illusions and he understands the caused vexation. Dr. Lohr's letter eliminates the personal bearings of the problem. However, some statements of the paper seem to deserve public consideration.

1. Contrary to Dr. Lohr's implication, no efforts have been made to estimate stroke volume from accelerographic excursions over the apex. Argumentation against such assumptions appears misleading.

2. The finding that the first systolic acceleration complex is not related to cardiac force only does not contradict earlier statements by other investigators. Studies on the effect of cardiac movements, hemorrhage, shock, and intracardiac pressure generation on various aspects of precordial movements advanced the understanding of their physiologic correlates. Such efforts were not destructive of clinical illusions because they confirmed previous statements based on clinical studies.

3. It is hard to see why the only way to interpret precordial acceleration correctly should be by relating it to precordial displacement.

4. Dr. Lohr and associates correlate displacement with acceleration by applying a multiple electronic differentiating technique, a highly sophisticated mathematical and physical operation. The validity of conclusions derived from such procedure are still open to debate, and the less than convincing similarity of Dr. Lohr's accelerograms to directly retrieved signal accentuates the need for reservation.

5. The comparison of accelerographic amplitude with the height of apex plateau has to be performed in awareness that a precordial bulge or heaving of long duration requires little, if any, change in the acceleration of the movement.

6. The source of the data stating that "the height of the apex cardiogram depends on diastolic aortic pressure" is unknown.

7. A similarity of precordial acceleration and displacement graphs in the 5 to 25 c.p.s. frequency range has been reported (Rosa). Numerous investigators observed a similarity between acceleration ballistocardiograms and precordial accelerogram. Such reports could hardly be interpreted as attempts to replace one technique by the other. The clarification of the validity and extent of such similarities will help to improve our understanding of graphic records.

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To the Editor:

Castellanos and Lemberg in their paper "The Relationship Between Digital and A-V Nodal Tachycardia With Block" in the AMERICAN HEART JOURNAL 66:605, 1963, suggest the use of the acetyl strophanthidin tolerance test as a guide to digitalis intoxication.

It is our feeling that this test should be used primarily in patients believed to be underdigitalized rather than overdigitalized. The fact that deleterious effects were evident even with small doses gives evidence of the dangers involved in giving further cardiac glycoside to the patient who may already be intoxicated.

We would urge that acetyl strophanthidin or other cardioactive glycoside not be administered under such circumstances until a trial of treatment for digitalis intoxication has been made.

Thomas N. Stern, M.D.

A disposable catheter for routine cardiac catheterization

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To the Editor:

The desirability of disposable medical equipment is well accepted. Such equipment is advantageous because of the reduction of the possibility of cross infection, elimination of pyrogens, decreased maintenance costs, and availability of optimal equipment for each procedure. Recent years have seen the advent of innumerable disposable items, the most important of which have probably been those designed for use with parenteral medications and infusions.

The advantages of a low-cost disposable cardiac catheter have long been recognized. The only radiopaque disposable tubing available at the time we became interested in disposable catheters that could be used routinely for right heart catheterization was the Swedish lead impregnated polyethylene. This tubing, although more opaque than the standard woven nylon catheters, is undesirable from two standpoints. There is not an adequate range of sizes, and the surface of the tubing is too rough. For these reasons, disposable catheters were used only for special purposes.

After consultation with several manufactures of medical plastics, bismuth loaded polyethylene and polyvinyl tubing was made available to us. The polyvinyl was discarded because of its lack of stiffness and its inability to maintain a preset curve. The polyethylene was satisfactory in all respects except radopacity. A more opaque polyethylene tubing* was made which exceeded the opacity of standard woven nylon nondisposable catheters as studied by cinefluorography in anesthetized dogs. The tubing is formed from virgin polyethylene especially compounded with 35 per cent bismuth oxychloride. This produces the desired radiopacity, yet maintains tensile strength, formability, and smooth lumen and exterior surfaces. The tubing has passed tests for acute toxicity, skin reactivity,

*Cardiovascular & Special Instrument Division, Becton, Dickinson & Co., Rutherford, N. J., medical grade heavy wall radiopaque polyethylene tubing.

and tissue sensitivity and neurologic tests. Burst pressures of closed-tipped catheters in which no side holes have been made have demonstrated that these catheters can easily withstand the range of pressures clinically used for injection of contrast medium. Catheters made from this tubing are easily shaped and maintain their preset curve since polyethylene does not soften at body temperature.

The tubing is first cut into a suitable length and a malleable stylette (copper wire) formed into the desired curve is inserted into one end. This end is immersed in boiling water for 1 minute and then cooled in tap water. Holes can be put into the curved end of the catheter with a catheter punch or a hypodermic needle filed for this purpose. The stylette is removed and the tip of the catheter is polished with a piece of cloth until there are no sharp edges. The opposite end of the tubing is flared over an open flame or with a flaring tool so that it can be fitted onto a standard female Luer Lok adapter designed for use with polyethylene tubing.

Closed-tip catheters are made in very much the same manner. After immersion in boiling water and cooling, the stylette is removed and the opposite end of the tubing flared. An adapter is put onto the flared end and a 10-c.c. syringe is fitted into the adapter. The tip of the catheter is heated in an open flame (alcohol lamp) and when sufficiently heated it swells. Negative pressure is applied with the syringe at this point with the tip of the catheter still in the flame. The softened end of the tubing is thus pulled into the lumen of the tubing. The catheter tip is permitted to cool in room air. After cooling for about 30 seconds the excess is trimmed with care taken not to cut off the sealed tip. The tip is then polished until smooth. Closed-tip catheters can be safely formed in this manner since polyethylene is a thermoplastic which melts like wax at about 300°F.[1] and when cooled solidifies into a homogeneous mass without degradation.[2] Multiple cross sections and longitudinal sections taken from the tips of the catheters formed in this manner have shown that the closed tips of the tubing are truly homogeneous.

About 3 mm. from the closed tip of the catheter a hole is punched in one wall and out the opposite wall with a catheter punch. Care is taken to keep the side holes no larger than two thirds of the internal diameter of the tubing in order not to weaken the tubing. We use a 17-gauge punch for tubing of 0.063 inches (1.575 mm.) internal diameter, 18-gauge for tubing of 0.054 inches (1.350 mm.) and 0.046 inches (1.50 mm.) internal diameter, 20-gauge for tubing of 0.039 inches (0.0975 mm.) internal diameter, and 23-gauge for tubing of 0.030 (0.750 mm.) internal diameter. It is important that the punch be sharp and that during the formation of the hole the punch be rotated to prevent roughening of the edges of the resultant holes. If the edges are roughened, they can be smoothed by polishing with cloth or fine sandpaper. The punch lumen is then emptied to insure that the punched-out catheter material is not in the lumen of the catheter. The catheter is then rotated 90 degrees and a second set of holes is made 2 mm. away from the first set. The catheter is rotated another 90 degrees and the procedure repeated, which results in three sets of holes, six in all. The catheters so formed are tested on the high-pressure contrast medium injector to be used to insure that the tubing will withstand more than the greatest pressure to be applied.

The polyethylene catheters are cold sterilized by standard techniques. In our laboratory we use Detergicide 1:1000 in 70 per cent ethyl alcohol. Prior to use they are rinsed thoroughly inside and out with sterile saline. If desired during the procedure, the curve in the disposable catheter can be altered aseptically by holding it in a stream of steam or by dipping it into boiling water.

Over 500 catheters of this type have been used in our laboratory. The opacity in infants and children catheterized with the use of an image intensifying unit has been equal to or better than that of the standard woven nylon catheters. The catheters handle well and do not become soft as do the standard woven nylon catheters. Injections of contrast medium using a pressure injector are comparable to those obtained with nondisposable woven nylon or Teflon catheters.

The price of these disposable catheters is approximately $.60, as compared to the price of standard woven nylon catheters with an open tip which are $6.00 and higher and the closed-tip woven nylon catheters which are in the range of $18.00. After use disposable catheters are discarded, eliminating maintenance cost which is considerably greater than that of making these disposable catheters. The metal Luer Lok adapters are cleaned and sterilized and then ready for reuse.

U. S. Catheter and Instrument Corp., Glens Falls, N. Y.

We are indebted to Mr. Paul Gould for his technical assistance.

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Marshall B. Kreidberg, M.D.
Harvey L. Chernoff, M.D.

Book reviews

THE CARE OF THE GERIATRIC PATIENT Edited by E V Cowdry Ph D Sc D (Hon) F R M S (Hon) Professor Emeritus of Anatomy Washington University St Louis Mo ed 2 St Louis 1963 The C V Mosby Company 566 pages Price $11 85

This is the second edition of this book which is edited by E V Cowdry The many contributors to the volume are prominent physicians but relatively few of them are primarily interested in geriatrics or gerentology Their interests in old patients are essentially of the sort expected of any physician Some of their experiences and ideas are interesting but their lack of a devotion to and special concern with gerentology and geriatrics as a speciality is evident from the discussions

Among the many aspects of geriatrics discussed are psychologic and psychiatric medicine cardiovascular orthopedic sexual urologic surgical nutritional and several others

The book is small in size and excellent in format and it should be of interest to doctors in practice Some of the presentations are very good

OCCLUSION OF CORONARY PERIPHERAL AND CEREBRAL ARTERIES MORBIDITY By L K Widmer Basel and J L Schelling Lausanne Basel 1963 S Karger 152 pages (In U S A Albert J Phiebig P O Box 352 White Plains N Y) Price $9

This volume gives the abstracts of the initial Congress of the Society of Angiology of Switzerland Dawber reports on the 8-year range of morbidity of the Framingham investigation From this a traceable correlation was found between morbidity from coronary disease and the elevation of the cholesterol level hypertension excessive use of nicotine altered vital capacity and elevated hematocrit and hemoglobin concentrations The presence of several of these factors at the same time leads to a definite increase in risk McDonald comes to the conclusion that in addition to other factors coronary thrombosis is induced by an increased blood clotting tendency since it was found that blood clotting ability is highly increased in coronary disease and especially in patients suffering from myocardial infarction Widmer reports on statistical research concerning the morbidity of peripheral blood vessel occlusions in 6 400 employed individuals who ranged in age from 15 to 64 years In comparison to the Framingham investigation it was shown that coronary and peripheral occlusions are of the same frequency and affect the same age group Two thirds of the patients did not recognize their illness Hutchinson reports on the influence of extracranial arteries on cerebral blood flow The data were collected from autopsy findings in 100 patients who died from cerebral ischemia Fifty-eight per cent of the showed stenotic or obstructed extracranial arteries Stricker reports on the changes in the cerebral arteries in different age ranges

In addition to all abstracts numerous discussions are reported This volume should be of interest to anyone working in the field of angiology

THE INCUBATION PERIOD OF CORONARY THROMBOSIS By G R Osborn M B B S (Melbourne) M R C P Pathologist to the Derbyshire Royal Infirmary London 1963 Butterworth & Co Ltd 190 pages Price $11

In these days of fashionable obsession with coronary atherosclerosis in rabbits rats and chickens it is refreshing to find someone who is still interested in the problem in man Conceding that Nature does not always employ controls suitable to satisfy the referees of a grant awarding agency she still performs some marvelous experiments It is a detailed examination of her work on the coronary arteries that Dr Osborn (a pathologist in England) concerns himself with in this book Applying a systematic approach in all his hearts he has examined sections of the coronary arteries obtained at regular intervals and cut serially when warranted from hundreds of patients dying of cardiac as well as of noncardiac diseases Not only is the preparatory approach systematic but so are his records of the histologic appearance of the coronary lesions for which he employs many original classifications

On the basis of a study of the hearts of 465 babies (and an even larger number of adults) he concludes that all the coronary arteries are normal at birth and therefore that heredity has little to do with the subsequent development of coronary disease Although this observation is of itself of great interest the conclusion about heredity is hardly reasonable since it must be based on the presumption that all hereditary influence was necessarily apparent as an identifiable morphologic change Even with universal normality of coronary arteries at birth however normal arteries were found to be uncommon by the age of 5 years and were rarely seen after the age of 15 Because of this Osborn suggests that the only fruitful approach to the prevention of coronary disease will be in the pediatric age group The initial pathologic changes (before age 5) were almost exclusively infiltration of mucin without any lipids whereas cholesterol and other lipids were present but still not of great importance in later years He does not believe that thrombosis or platelets play any significant role in the development of atheroma

Two morphologic changes are interpreted as being clinically grave complications One is the secondary vascularization of coronary lesions which Osborn considered the *sine qua non* for the development of clinical manifestations and the second is rupture of certain atheroma (which he refers to as atheromatous abscesses) Since

the vascularization appears as one of the later manifestations in the pathogenesis of coronary lesions, it is difficult to attribute all the danger to it rather than to concurrent late developments, such as degeneration of the central portion of the atheroma. Furthermore, to balance against the danger of intramural hemorrhage from these new vessels, we must consider that some of them act as intracoronary anastomoses which bridge the point of local obstruction and thus preserve flow into the distal lumen of the artery. As for the rupture of atheroma with peripheral embolization of the content, there is little question of the serious consequences of such an event, which Osborn indicates is a far more common occurrence than is presently appreciated.

In addition to a generous number of excellent photomicrographic illustrations which accompany the text, there is a fine chapter by K. F. Davis, an engineer, who discusses the hemodynamics of the coronary circulation on the basis of Osborn's description. Little can be said for Osborn's concluding chapter discussing future research, which is disjointedly written and detracts from the rest of the book. Many may disagree with Osborn's ideas, but in view of the volume of his material and the apparent logic with which he has thought about some careful observation, no physician can afford to ignore him. In time, other investigators will surely confirm or refute his interesting concepts. If he is wrong, those who disprove his interpretations can still profitably use his basic data. If he is right, this book will deserve a secure place on the shelf beside the classics on heart disease.

CLINICO-PATHOLOGICAL CONFERENCES OF THE MOUNT SINAI HOSPITAL. Edited by Fenton Schaffner, M.D., Associate Attending Pathologist and Assistant Attending Physician; Hans Popper, M.D., Pathologist in Chief; and George Baehr, M.D., Consultant Physician, all of the Mount Sinai Hospital, New York, 1963, Grune & Stratton, Inc., 314 pages. Price $[illegible].50.

This volume is composed of 73 selected C.P.C.s from the Mount Sinai Hospital which deal with pulmonary, cardiovascular, renal, gastrointestinal, and hepatic problems of predominantly nonsurgical interest. The clinical discussion of each case is excellent and is usually vigorously participated in by two or more clinicians, providing a stimulating emphasis on critical differential diagnosis. Detailed and valuable radiographic analysis is noteworthy, especially in the pulmonary cases. The pathologic changes are well illustrated and serve as an adequate basis for relating the clinical picture to anatomic changes. Perhaps some anatomic points are presented with an excess of dogmatic zeal, lacking is a little of the flare for presenting uncertainties in a provocative and yet informative manner. These cases have been well selected and present some unusual diseases as well as interesting aspects of the more common disease. Pertinent references are appended to each presentation. The whole collection is a valuable one: educational for the student, informative for the experienced clinician and pathologist, and stimulating to the researcher.

Announcements

A POSTGRADUATE SEMINAR entitled EVOLVING CONCEPTS IN PULMONARY DISEASES will be presented on March 18-21, 1964, by the Department of Radiology of the University of Miami School of Medicine and Jackson Memorial Hospital.

For information concerning the seminar, contact the Director, Raymond F. Parks, M.D., Professor and Chairman of Radiology, University of Miami, Coral Gables, Fla., or the Chairman of the Scientific Program Committee, Manuel Viamonte, Jr., M.D., or the Chairman of the Registration Committee, Robert F. Feltman, M.D.

THE AMERICAN SOCIETY FOR ARTIFICIAL INTERNAL ORGANS will hold its 1964 Annual Meeting and Scientific Sessions on April 12 and 13, 1964, at the LaSalle Hotel, Chicago, Ill.

In charge of arrangements is Dr. Bert K. Kusserow, Secretary-Treasurer, American Society for Artificial Internal Organs, Department of Pathology, University of Vermont College of Medicine, Burlington, Vt.

American Heart Journal

April 1964 Volume 67 Number 4

Editorial

Intractable heart failure— Management with 5 to 7 days of fasting A preliminary trial

*Arthur J. Merrill, M.D.**
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At times digitalization, bed rest, low salt diet, and diuretics no longer suffice to maintain compensation in patients who are in heart failure. The body begins to retain water, which in the salt-restricted subject leads to the so-called "sodium dilution syndrome." This is recognized by cardiologists as the terminal phase in patients with fixed severe chronic heart failure. Several drastic measures have been applied in this situation, including drainage of edema with Southey tubes, water restriction, and a no-sodium regimen. A no-sodium diet is of little value in this condition, usually aggravates the symptoms, and induces nausea, vomiting, weakness, drowsiness, and even coma. Water restriction leads to overpowering thirst, and patients have been known to remove flowers from a vase and drink the stinking water from it. Why patients are thirsty when the sodium concentration of the extracellular fluid is low is an unsolved mystery. Retention of solids other than sodium from the low renal blood flow and glomerular filtration rate could be one factor, and change in intracellular osmotic forces has been suggested. Low cardiac output associated with other conditions, such as shock, is known to produce thirst. Regardless of cause, the thirst makes water restriction difficult and even cruel. Southey tubes are uncomfortable, may lead to infection and phlebitis, and only rarely seem to afford any durable relief.

In the search for a more successful and less harrowing program of management for these patients, Dr. Walter Bloom's regimen of fasting drew my interest. Bloom found that loss of weight during total fast with free access to water far exceeded that expected from tissue consumed for energy needs. First, the average individual is estimated to lose roughly ½ pound a day at rest for energy requirements, or 2½ pounds in 5 days. One of Bloom's fasting subjects lost 16 pounds in 5 days, and the average daily loss of his 10 original subjects ranged from 1.8 to 3.5 pounds per day.[1] Secondly, further study revealed that this discrepancy between actual loss of weight and the loss calculated for daily energy requirement could be accounted for by excretion of salt and water. The loss of salt was a surprise, since these patients were on a salt-free intake and would be

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iron deficiency (3) albuminuria from chronic passive congestion of the kidneys. The administration of NaCl and daily thiazide diuretics was stopped. Water was to be limited to 300 ml. daily plus the volume of the previous day's output. However, the patient was incontinent and circumstances were such that accurate intake and output were unobtainable, so that it was decided to try a regimen of fasting with free access to water. Had it been realized that the change would be so spectacular, a more strenuous effort would have been made to obtain accurate intake and output data with an indwelling catheter, as well as 24 hour excretions of sodium, but the patient was thought to be moribund. The diet was started on July 20, 1962, at which time she weighed 141 pounds. Progress is shown in Table I. After returning home the patient continued to improve, and her son reported that she was alert except for lapses of memory, and was able to be up and about without dyspnea or edema. The urine contained a trace of albumin. Although her improvement could have started coincidentally with the fasting regimen, she was getting steadily worse until the time it was started, and her improvement began within 24 hours afterward.

Two other patients with severe congestive heart failure have been tried on this regimen. One showed an excellent response. The other exhibited very little change. The latter however was jaundiced possibly from a combination of congestive heart failure with pulmonary emboli, and had a low serum albumin.

This problem needs to be studied further with controlled observations on more patients who have advanced failure and the sodium dilution syndrome. These preliminary attempts and fragmentary reports are encouraging, and seem worth following through by physicians engaged in active research.

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Clinical communications

Clinical features relevant to possible resuscitation in death after acute myocardial infarction

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David I. Miller, M.D.
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Many patients who die soon after an acute myocardial infarction demonstrate a paucity of pathologic changes in their myocardium.[1-6] Partly responsible is the fact that a certain amount of time is required before either the gross or microscopic changes secondary to acute coronary ischemia become apparent. However, even when the acute lesions are discernible, the frequent occurrence of old scars comparable in extent to the fresh ones and the finding of more advanced coronary abnormalities in patients who die of other causes reinforces the impression that the myocardium as seen at necropsy appears to be capable of continued adequate function.[4-6] The clinical counterpart of these observations has been aptly characterized by Beck as "hearts too good to die."[7-9] Support for this viewpoint is appearing in the form of case reports which describe successful resuscitation of patients after ventricular fibrillation associated with acute myocardial infarction.[10-16]

The possibility of reversing the course of a fatal heart attack in some patients is now a universally accepted concept. What remains unknown is the frequency with which this result might be expected. This in turn is related to both the reversibility of ventricular fibrillation and the efficacy of our therapeutic measures. At present only a few answers are available. One of these which may be noted in most of the case reports referred to above[10-16] is that success is most likely when the interval is *smallest* between the onset of cardiac arrest and the institution of resuscitative measures. Ideally, then, every patient sustaining an acute myocardial infarction should be placed under continuous surveillance for the period of time during which a fatal arrhythmia might occur. Furthermore, such monitoring ought to be carried out in an area in which trained personnel and specialized equipment are available should resuscitative measures be needed.

Because many hospitals are not equipped to supply such service to every patient admitted with a coronary occlusion, because these serious arrhythmias occur only in a small per cent of the group, and because there are certain inconveniences associated with continuous monitoring of long duration, it seemed to be worth while to analyze

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our clinical experience with a view toward identifying those patients who are most likely to succumb and the time interval during which the untoward events might occur. If these were known, the high risk cases could be placed under closer observation in a *coronary care unit* during the danger period. Other clinical features which might influence the effectiveness of resuscitation have also been considered.

Material

From Jan. 1, 1959, until Dec. 31, 1961, 1,101 patients with a diagnosis of acute myocardial infarction were treated at Sinai Hospital, and of these, 191 patients died. After reviewing the clinical records of these deaths, we omitted 100 cases from the present study for one of the following reasons: (1) The coronary occlusion occurred after surgery or in association with some other major illness. (2) The diagnosis was not clearly established clinically nor confirmed at postmortem examination. (3) The recorded information was not sufficiently complete. Since we were interested primarily in those who might be resuscitated, 5 patients with rupture of the myocardium were also excluded. In addition, 81 patients who were admitted to the emergency room with a presumptive diagnosis of acute myocardial infarction died within a short period of time. Even though most of these diagnoses were undoubtedly correct, data in these cases were necessarily limited, and only 47 patients satisfied two of the three criteria which we thought were necessary for inclusion in the study, e.g., the history was compatible with the diagnosis, the serum transaminase level was elevated, or the electrocardiogram suggested an acute infarction. Therefore, the 138 cases analyzed represent those patients who died as the result of a definite acute myocardial infarction uncomplicated by concurrent illnesses.

Definition of terms

Patients who die of this disease exhibit one of three patterns of clinical behavior. One group dies suddenly, and the terminal event is accompanied by an arrhythmia which lasts for minutes or as much as an hour. When the interval between the onset of chest pain and death is so brief that the patient only reaches the ambulance or the entrance to the emergency room, there is no opportunity to confirm or diagnose the arrhythmia. However, when these patients live long enough to be admitted to the emergency room, or when the abrupt change for the worse is noted while the patient is convalescing in the hospital, an electrocardiogram usually records the presence of premature ventricular contractions, ventricular tachycardia, or even ventricular fibrillation. These cases of "self electrocution"[3] have been designated here as *rhythm deaths*. In 26 of these 77 cases, an electrocardiogram was taken either at the time of sudden death or usually within a few minutes after cardiac arrest had been recognized. Twenty-four tracings showed ventricular fibrillation, one asystole, and one idioventricular rhythm. In addition, 11 electrocardiograms showed ventricular tachycardia; this occurred within 24 hours of death in 7 cases. A second group of patients have their clinical course characterized by an inability to maintain a blood pressure. This may be noted shortly after the onset of symptoms or at a time during convalescence when progress seems to be satisfactory. The response to intravenous vasopressors is usually short lived or nonexistent, and death occurs within hours to several days. Although abnormal rhythms may be seen during the critical period, the precipitating and prominent feature is the hypotension, and these cases are called *shock deaths*. The third group is one in which the symptoms and signs of congestive heart failure appear at some time during the illness and result in death after a period of deterioration usually lasting up to several days. These are referred to as *failure deaths*. Occasionally, more than one clinical feature appears to contribute significantly to the fatality. For example, a patient suffering from congestive heart failure may show an associated arrhythmia or hypotension. Usually, it is possible to decide from the history and physical findings which is the primary derangement. The only unclear circumstance is when both shock and arrhythmia are noted upon the initial examination. These cases were arbitrarily assigned to the *rhythm group* even though either one of these disturbances may precipitate the other.

Data

Mode of death This matter has been analyzed by a number of authors during a review of their mortalities following acute myocardial infarction [2,17,21] What we have chosen to call *rhythm deaths* have been described by others as sudden un expected, or mechanism deaths The findings are summarized in Table I and fall into a surprisingly narrow range de spite the many factors which tend to favor some variation For example the inclusion of emergency room cases would influence the results As mentioned above we ex cluded 34 of our 81 emergency room cases because during the brief illness sufficient clinical data could not be obtained to sup port the diagnosis of acute myocardial infarction However necropsy studies re ported by others indicate that the great majority of these sudden deaths are due to coronary artery disease [4,5] If we had in cluded these cases as *rhythm deaths* the value for this category would have been increased by 10 per cent Other factors which might influence consistency between reported series are the hospital from which the material is collected the criteria which the authors accept to confirm the diagnosis and the percentage of autopsies performed This latter feature would increase the accuracy of the sudden death group by removing the small number of cases in which death was due to myocardial rupture or pulmonary embolism rather than to an arrhythmia The average for the 7 studies listed (692 cases) indicates that about one half of those patients who die during the course of an acute myocardial infarction succumb to arrhythmia whereas one third die of congestive heart failure and one sixth as a result of circulatory collapse

Effect of age and sex The sex of the pa tient sustaining a fatal myocardial in farction did not alter the manner by which death occurred Table II illustrates that age did not influence the likelihood of a patient dying a *rhythm death* nor did older patients die more frequently in shock This appears to be true whether one considers the older group as being over age 60 or over age 70 However with increasing age the incidence of heart failure rises from 16 per cent in the younger patients to 32 per cent in those over 60 years of age and to 40 per cent in those over 70 years The likelihood of a difference as large as this occurring as a result of chance is only 1 in 16 ($p = .06$) when those under and over 60 years of age are compared The data are more significant for those over 70 years ($p = .02$) This finding is not unexpected since more myocardial fibrosis would be anticipated in the older group and any further destruction of muscle would lead to failure The surprising fact is that the incidence of *failure deaths* (40 per cent) is not even greater in those patients over 70

Influence of previous cardiac disease The past history of these patients might be expected to give some clue as to the type of death that should occur The pres

Table I Mode of death in patients succumbing during an acute myocardial infarction

Authors and year	Number of cases	Type of death		
		Rhythm (%)	Failure (%)	Shock (%)
Levine and Rosenbaum [7] (1941)	80	35	20	—
Woods and Barnes [8] (1942)	60	53	25	—
McCain et al [9] (1950)	95	26	35	22
Ball et al [2] (1955)	89	65	31	4
Achor et al [3] (1956)	157	50	42	—
Hellerstein and Turell (1958)	73	40	60	—
Present study	138	56	27	17
Total series	692	47	34	—

All th values do ot add up to 100 per cent since other less f eq ent causes of death which may ha bee li ted by the uth rs re t i 1 ded

Table II. Effect of age on the mode of death

Age	Number of patients	Type of death: Rhythm		Failure		Shock	
		Number	Per cent	Number	Per cent	Number	Per cent
Under 60 yr	43	28	65	7	[illegible]	8	19
Over 60 yr	95	49	51	30	32	16	17
Over 70 yr	48	23	48	19	40	6	12
No age selection	138	77	56	37	27	24	17

Table III. Influence of previous heart disease on mode of death

Past history	Number of cases	Type of death: Rhythm (%)	Failure (%)	Shock (%)
Angina pectoris				
Present	45	67	24	11
Absent	68	50	28	22
Heart failure				
Present	26	54	31	15
Absent	8	57	23	20
Myocardial infarction				
Present	51	[illegible]	23	16
Absent	65	55	29	15

ence of angina pectoris in patients with arteriosclerotic heart disease suggests severe coronary sclerosis and marginal blood flow, prior congestive failure indicates that the heart muscle already has shown signs of ineffective pumping, and the occurrence of one or more previous infarctions denotes that varying amounts of muscle have already been replaced by scar tissue. Thus among the fatalities those patients without previous heart disease might be more likely to die a *rhythm death* than those who are known to have had previous muscle destruction. The results listed in Table III show that 45 of 113 patients gave a history of angina pectoris, 26 of 113 patients had previously been in heart failure, and 51 of 116 patients had sustained one or more prior myocardial infarctions. No effect was noted upon the mode of death when the data were analyzed with respect to the presence or absence of the preceding symptoms using the chi square calculation with two degrees of freedom. Even when heart failure or myocardial infarction had occurred previously, the likelihood that these patients would die in heart failure was not increased.

Duration of illness. This determination seemed important, first, from the viewpoint of the danger period during an infarction and, second, to learn whether one variety of death occurred at one time rather than at another. The values were obtained by the summation of the duration of symptoms prior to admission and the days in the hospital. Occasionally, the exact time of onset of the acute infarction was not clear, and for this reason the period of hospitalization may be of greater value in selecting the time for close observation. In general, the shortest illnesses occurred

in those patients in whom the prominent feature of the illness was arrhythmia (average of 5.0 days) or hypotension (average of 5.3 days). Patients who died of heart failure had an average illness of 10.4 days. The periods of hospitalization in days were 3.7, 3.5, and 7.2, respectively. In Table IV the duration of the illness and the hospitalization are divided into periods consisting of the first 5 days, the period from 6 to 10 days, and the period greater than 10 days. In each mode of death the early period is the most critical time, although 36 per cent of the patients who died of congestive failure succumbed more than 10 days after the onset of their symptoms. Twenty-seven per cent of this group were hospitalized more than 10 days. More significant, however, is the fact that 74 per cent of all the deaths occurred within a 5 day period of hospitalization.

Value of the admission findings. The physical findings obtained at the time of admission were scrutinized in order to find any abnormalities which might indicate that death was imminent and what type of death might be expected. A few cases of severe shock and congestive failure were noted in which the fatal outcome was anticipated on the initial examination. However, in the majority of instances such predictions were not possible. The initial blood pressures and the presence of congestive failure were analyzed as to their correlation with the mode of death. In Table V it may be seen that when patients with similar initial blood pressures are compared one cannot foresee how death will occur. The presence of hypertension would appear to eliminate the *shock* variety of deaths, but there were only 13 patients with this finding on admission. In the 40 patients who were found to have hypotension upon admission, the distribution of deaths appears to be similar to that for the total group. However, nearly all the patients in this category who died a *rhythm death* also had shock. These were the patients admitted with both arrhythmia and hypotension who were arbitrarily assigned to the *rhythm* group. Thus, even though 57 per cent of the hypotensive patients died because of an arrhythmia, it is important to note that in 31 of the 40 patients admitted with hypotension shock remained prominent during the illness. Fifty-nine patients were found to have some degree of congestive heart failure. Although in many this condition improved with treatment, a smaller than expected number of *rhythm deaths* was seen. The occurrence of *failure deaths* in this group with failure on admission was 51 per cent as compared with 27 per cent in the unclassified group. This difference is highly significant ($p < .001$).

Usefulness of the electrocardiogram. Since one or more electrocardiograms had been recorded for nearly all patients, it seemed to be worth while to correlate signs of myocardial irritability and the presence of conduction blocks with the clinical course. Myocardial irritability refers to an ectopic focus or ectopic pacemaker in the

Table IV. Duration of illness and hospitalization in patients who died with an acute myocardial infarction

Category	Type of death: Rhythm (%)	Failure (%)	Shock (%)
Duration of illness			
5 days	72	42	68
6–10 days	8	22	5
Over 10 days	20	36	27
Duration of hospitalization			
5 days	77	65	75
6–10 days	6	8	17
Over 10 days	17	27	8

Table V. Admission findings as related to mode of death

Findings	Type of death		
	Rhythm (%)	Failure (%)	Shock (%)
Hypertension	69	31	0
Normotension	52	31	1
Hypotension	57	18	25
Heart failure	34	51	15

Table VI. Association of electrocardiographic changes with the mode of death

Description	Type of death		
	Rhythm (%)	Failure (%)	Shock (%)
Atrial irritability	48	27	25
Supraventricular irritability	48	35	17
Ventricular irritability	9	21	0
No conduction defect	58	21	21
Auriculoventricular block	53	35	12
Intraventricular block	42	46	12

atrial or ventricular muscle. The location of the infarct was not considered, since others had examined this feature with regard to prognosis and type of death.[18] Even in the absence of electrical indications of irritability (63 patients) or a conduction abnormality (86 patients), about one half of the patients died with an arrhythmia (Table VI). Among patients who showed intraventricular block, an increased number (46 per cent) died of congestive heart failure. The transaminase levels for the groups with and without these conduction disturbances were compared in order to see whether patients with septal involvement tended to have larger infarcts. No such correlation could be found. Perhaps the most striking finding—even though not too surprising—is the fact that 79 per cent of the patients who showed ventricular irritability died a *rhythm death*. No patients who had ventricular irritability died in shock, possibly because the faster supraventricular rates associated with shock tend to suppress ventricular irritability. There were a small number (14 patients) in whom both supraventricular and ventricular irritability were noted on the electrocardiograms, and these patients appeared to resemble the above-mentioned group with supraventricular irritability, although the size of sample probably does not justify any binding conclusions.

Influence of transaminase levels. Measurements of serum transaminase were made in 86 patients, and the highest recorded value for each was tabulated as being normal (less than 40 units), moderately elevated (40 to 100 units), or high (over 100 units). Table VII illustrates that transaminase levels were distributed equally among the patients who died *rhythm* and *shock* deaths, but that 52 per cent of those who died in congestive heart failure had high values. Since many patients who died *rhythm* or *shock* deaths died early after the onset of their acute infarction, the finding of normal or moderately elevated transaminase levels does not permit one to estimate the size of the infarct. If death had not intervened, the values might have been much higher. On the other hand, patients who died in congestive failure tended to live longer after the onset of their final illness and thus allowed the transaminase values to develop fully and more accurately reflect the amount of muscle destroyed. Because of this requirement that a certain amount of time is necessary before the serum transaminase level can help one estimate the extent of the infarction, these determina-

Table VII. Relation of serum transaminase levels to the mode of death

Transaminase values	Type of death		
	Rhythm (%)	Failure (%)	Shock (%)
Normal (less than 40 units)	37	0	[illegible]
Moderately elevated (40-100 units)	29	19	[illegible]
High (over 100 units)	34	52	[illegible]

tions may only be helpful when they are markedly elevated early in the illness Under these circumstances the clinician should be alerted to the possibility of death occurring although the mode of dying cannot be inferred

Discussion

In previous years the clinical features of acute myocardial infarction have been examined carefully for the purpose of increasing both diagnostic accuracy and prognostic capability Although interest in therapy has attracted the attention of all little progress has been made in altering the natural course of events except for the introduction of vasopressor therapy in those cases in which shock accompanies myocardial infarction Recent advances in resuscitative techniques have suggested the possibility of reducing the mortality still further by restoring some of those patients who sustain fatal heart attacks Attention should now be focused upon those clinical manifestations which might indicate (a) impending death (b) the kind of death that might be expected and perhaps (c) the type of patient who is restorable

A number of authors have pointed out that death occurs suddenly in from 35 to 83 per cent of these patients[3 17 1 8] the variation being related primarily to the type of cases included Thus reports from a renowned clinic to which patients are referred might be expected to show fewer sudden deaths than those from active municipal or community hospitals Although many emphasize that death is often sudden fewer have described just when the terminal event occurs during the illness Friedberg[3] states that most deaths occur within the first week a large per cent within 48 hours In one series[20] 23 per cent of the deaths took place within 24 hours of onset whereas among the soldiers studied by Yater and associates[1] 83 3 per cent died during the first day 52 9 per cent within the first hour of the onset of symptoms Our experience which probably resembles that of most general hospitals reveals that 74 per cent of the fatalities after acute myocardial infarction occur within the first 5 days of hospitalization Therefore the placement of all patients with acute infarction into a *coronary care unit* with continuous monitoring for a 5 day period should under ideal circumstances allow the immediate recognition of cardiac arrest in 3 of 4 patients who succumb

The recognition of the other 26 per cent of patients who die later in the course of their illness remains a problem One approach—but probably an impracticable one—would be to keep all of these patients continuously monitored for the total period of hospitalization A more reasonable solution might be to return these patients to the *coronary care unit* after the initial 5 day period when events in their illness suggest that trouble may be anticipated Such occurrences include a return of or sudden increase in chest pain a drop in blood pressure or the reappearance of electrocardiographic signs of ventricular irritability That these changes represent danger is known but not sufficiently emphasized What remains unknown is the question of how often detectable premonitory warnings appear and for how long in patients who subsequently die of their acute infarction

Summary

The clinical course of 138 patients who died after an acute myocardial infarction have been reviewed with the aim toward elucidating those features which might influence the possibility of resuscitation The majority of the deaths occurred unexpectedly presumably as the result of an acute arrhythmia Failure of the heart to function adequately as a pump was noted in 44 per cent—three fifths of these patients died from congestive heart failure and two fifths from circulatory collapse Seventy four per cent of the deaths occurred within a 5-day period of hospitalization

The sex age and presence of previous cardiac disease showed no association with the manner of dying Patients over 70 years of age did not die more frequently in shock but did die from congestive heart failure slightly more often than expected Even when the past history was positive for previous heart failure or infarction the likelihood of death occurring in heart failure was not increased

investigations have likewise demonstrated that the risk of having, and of developing, coronary disease increases with the level of serum cholesterol.[7,8] Regardless of the importance of focusing major attention on the precursors of coronary disease, there is an unfortunate tendency at times to equate the genetic aspects of coronary heart disease, or for that matter atherosclerosis, with the genetic aspects of hypercholesterolemia. In a study of the hereditary aspects of coronary disease, a second point of departure should be the investigation of aggregations of the disease itself in kindreds of index cases representative of the population at large. Only through such an approach can the over-all importance of genetic factors in atherogenesis be assessed. At the same time, more is to be learned from investigations among special and selected groups, such as families with hypercholesterolemia, since these groups offer outstanding opportunities for research into intimate pathogenic mechanisms. These latter studies will not, however, yield an answer to the question whether genetic influences contribute significantly to the burden of these disorders as they present themselves in the general population. Therefore, a review of those studies which tend to provide tentative estimates of these influences will be presented. This review will make it apparent that there is a need for further and more extensive studies and that, so far, there is inadequate evidence for taking a strong stand on whether genetic factors are or are not of *major* importance in the development of the atherosclerotic diseases. In the making of this statement there is no attempt to belittle the significance of such factors. The attempt is to show the need for buttressing the evidence.

A. Studies among relatives of patients and controls. Most cardiologists have no doubt that they see not infrequently patients with coronary disease whose parents or siblings are similarly affected.[9] At the same time it would be important to know the extent to which such instances are representative of the total experience among *all* the patients who are seen over the years. Moreover, a disease which in the United States affects in a clinically demonstrable fashion as many as 5 per cent of middle-aged men[10] and is the cause of death in about 40 per cent of middle-aged men who die[11] (not to mention older men) can be expected to coexist by chance in members of the same family with appreciable frequency. In addition, the experience of cardiologists, hospitals, or clinics is not necessarily representative of events in the population at large. Finally, the diagnosis of coronary heart disease is by no means always simple, nor is information on all family members readily obtained or, if obtained, always reliable. It is easy, therefore, to find flaws in the data about to be reviewed but difficult to collect information which is better. In fact, the difficulties are such that the scarcity of accurate and representative data on familial occurrence of coronary disease is not surprising.

Gertler and White[12] analyzed the family histories of 97 male patients who developed coronary heart disease prior to the age of 41, and compared them with those of 146 male control subjects. It is important that absence of hypertension was a criterion for selection in the patients. Disease of the coronary arteries was twice as common a cause of death in the fathers of the patients as in the fathers of the control subjects (37 vs. 19 per cent); among the mothers the corresponding trend was less marked (10 vs. 7.7 per cent). Nine per cent of the sibs of patients died of coronary disease as opposed to 1 per cent of the sibs of controls. Gertler and White searched for multiple cases in the 100 sibships. There were 8 sibships with multiple cases of coronary disease; in 1 of the 8 there were 3 cases including the index cases, and in the other 7 there were 2 cases in the sibship. Gertler and White summarize this situation among siblings as follows: "The genealogies are interesting in that they fail to show a spectacular number of family members with coronary heart disease." This statement is of particular interest since it is becoming increasingly clear that familial aggregations need not be striking in order to be significant and meaningful. In fact, follow-up study on these patients suggests that the familial factor is, in fact, very important in these groups,[13] and subsequent analysis of the original data indicates that a positive family history carries appreciable weight.[14]

Thomas and Cohen[15] reported on the

frequency of coronary heart disease, hypertension, obesity, and diabetes in parents, grandparents, uncles, and aunts of 266 consecutive medical students at Johns Hopkins University.[11] The information, as in the study by Gertler and White, was based on carefully collected and reviewed medical histories. The major findings may be summarized as follows. First, the frequency of coronary disease in the sons and daughters of the grandparents of the students was analyzed, representing the parents, uncles, and aunts of the students themselves. When both grandparents had coronary disease, 21.2 per cent of their sons were similarly affected; when neither grandparent had the disease, only 4.1 per cent of the sons were reported to have the same condition. For matings of one affected and one unaffected grandparent, the frequency of coronary heart disease among their sons fell in between, being 8.2 per cent. Among the daughters of grandparents, the trend was in the same direction but less steep. The data may also be viewed in a different way: of 43 sons with coronary disease, 26 (60 per cent) were the offspring of grandparents of whom one or both were similarly affected. Next, the frequency of coronary disease among siblings of the students' parents was estimated. When the students' fathers were affected, his brothers showed a frequency of coronary disease of 15.8 per cent, about 4 times more than when the fathers were free from coronary disease. Coronary disease was also more frequent among the sisters of affected fathers. There were too few siblings of affected mothers to provide meaningful data. In general, data of this nature are in part conditioned by the age of the propositus: the older the propositus, the greater the chances of finding an affected relative.

Medical students at Johns Hopkins University cannot be considered to be a representative segment of the general population any more than were the patients or controls in Gertler and White's series, even though in the former case there was no deliberate exclusion of hypertensive subjects or limitation of age range. Nevertheless, the trend is similar in both studies, although one would not be justified in comparing the magnitude of the trend in view of methodological differences. Rusek and Zohman[16] also compared the frequency of a history of cardiovascular disease among the parents of 100 patients with coronary disease and that among the parents of 100 control subjects without differentiating between the types of cardiovascular disease as was done in Thomas' study; the frequency of a positive history was 67 per cent in one or both parents of patients, as compared with 40 per cent among the control subjects.

The most recent data were reported by Shanoff and associates[17] on the basis of a random sample of 102 patients and 100 controls drawn from patients who attended the Veterans Administration Hospital in Toronto. Thirty per cent of the patients but only 20 per cent of the controls had an affected father; a similar gradient was observed for mothers of patients and controls. The brothers of the patients were significantly more often affected than were the brothers of the controls; although the trend for their sisters was the same, the difference was not significant. It is of considerable interest that the disease became manifest in the sons on an average of 20 years earlier than in their fathers, which suggests that environmental changes over the past few decades may have tended to bring a genetic predisposition increasingly into the open.

B. Studies among special groups. It is well known that life insurance companies have long been aware of the significance of positive family histories. As an example, the experience of 27 companies on about 18,000 lives over a span of 15 years is cited as reported by Levy.[18] Persons insured at standard premium who report two or more cases of early cardiovascular renal disease in their families have an excess risk of 75 per cent of dying of heart and circulatory diseases and an excess risk of 80 per cent of dying specifically of coronary heart disease.

In many ways studies on twins are ideally suited to establish the existence of genetic factors, although twins, even if reared apart, may still share etiologically significant environmental influences which may account in part for similarities between them. There are few such studies relating to coronary heart disease. Harvald and Hauge[19] analyzed data on 3,100 + of twins in Denmark. Among 82

60 years of age the concordance rate for deaths from coronary occlusion was the same for monozygotic twins and dizygotic twins whether of the same or opposite sex which suggested to the authors that genetic factors generally speaking play only a minor role in the etiology of coronary arteriosclerosis. However Verschuer[8] found a concordance rate of 19.0 per cent for coronary sclerosis among 21 pairs of monozygotic twins as compared with a rate of 8.5 per cent in 47 pairs of dizygotic twins. Benedict[1] reported on a pair of identical female twins who developed symptoms and signs of coronary insufficiency at about the same age in their early forties blood pressure and total serum lipids and cholesterol were well within normal range in both twins. Lees and coworkers[22] studied a pair of identical male twins one of whom developed a myocardial infarction at the age of 27 detailed biochemical investigations suggested a defect in lipid metabolism.

The findings of Stare and his group on the frequency of coronary disease in Bostonians from Ireland and their brothers who stayed in the home country will be of much interest.[3] Such investigations and others in progress will eventually help in segregating environmental from genetic factors in familial studies of coronary disease.

Scattered throughout the literature one finds other data relative to familial aggregations of coronary heart disease on families with xanthomatosis or frank hypercholesterolemia. All these studies in addition to those just reviewed support the belief that coronary heart disease does in fact have a tendency to aggregate among blood relatives. From the point of view of segregating environmental from genetic factors it would be of interest to have corresponding data on spouses but these are lacking. In general as Ciocco has reported[24] spouses tend to die of similar diseases whether on account of sharing the same environment or associative mating.

Mechanisms of genetic transmission

A. Serum cholesterol and blood pressure levels. On the basis of clinical observation it has been known for a long time that hypertension and hypercholesterolemia are frequently found among patients with coronary disease. One of the major if not the major single contribution of epidemiological research in this area over the past 10 or 12 years has been the establishment of statistical proof for these observations in representative segments of the population and the accumulation of data which permit a quantitative as opposed to a qualitative estimate of these relationships. Thus it can be calculated from the Framingham data[19] that no less than about two thirds of the subsequent cases of coronary heart disease have cholesterol levels of 260 mg. per cent or over blood pressure of 160 and or 96 mm. Hg or over or a combination of the two. Since a genetic factor is involved in the control of both serum cholesterol and blood pressure levels and since coronary disease is 3 or 4 times more common in middle aged men when one or both of these factors are in the upper range than when they are not it must inevitably follow that coronary disease will aggregate in families. A calculation based on a population model shows that two thirds of the aggregation of coronary disease in male siblings might be accounted for by the known familial trends in cholesterol and blood pressure levels.[14]

This important topic cannot be discussed without mention of the question whether blood pressure and cholesterol levels are determined by single genes or multiple genetic and environmental agencies. The estimate of genetic influences is of course much easier if only single genes are involved and if the frequency of this gene in the population can be determined. There seems to be little doubt at this stage that it is extremely difficult if not impossible to demonstrate bimodality in the distribution of either blood pressure or cholesterol.[14] This in itself is no proof that bimodality might not be hidden within these skewed distributions. In fact Cicchinelli[3] has derived a procedure based on the method of maximum likelihood which permits with the aid of a computer the dissection of any skewed curve into two separate Gaussian distributions and he has applied this procedure to blood pressure data from two epidemiological studies. While the biologic as opposed to the mathematical significance of this work

awaits confirmation it opens a new approach to the study of this problem For the time being from a purely practical point of view it must be accepted that it is not possible to indicate the degree of probability of any given blood pressure or cholesterol level to be within the normal or abnormal distribution if such does indeed exist

A preliminary view of our own data from the Tecumseh study to be described later tends to support the belief that both serum cholesterol and blood pressure levels are determined over the whole range of the distribution by multiple genetic and environmental factors [8] These findings are in accordance with the data of Miall and Oldham[29] on blood pressure correlations in propositi and their first degree relatives and the data of Schaefer Adlersberg and Steinberg[30] and our own previous reports[4] in regard to serum cholesterol levels In our recent studies [8] serum cholesterol and blood pressure levels in parents and children in the town of Tecumseh were plotted by sex and 10 year age groups in parents and 5 year age groups in children using a computer which calculated means intercepts slopes and correlation coefficients at the same time A summary of the correlation coefficients for cholesterol values in parents and their children (fathers vs sons fathers vs daughters mothers vs sons mothers vs daughters) indicates that 31 of the 39 correlations were based on 50 or more observations Twenty three of these 31 coefficients were significantly different from zero at the 5 per cent or 1 per cent level Although the correlations are low generally of the order of about 0 2 it is noteworthy that most of the slopes of the regression lines had a positive value indicating a regular although not strong tendency for parents and children to resemble each other over the *whole* range of the distribution rather than just in the upper range since their regressions could be shown to be essentially linear For systolic blood pressure a similar picture prevailed although the correlation coefficients tended to be somewhat lower than those for cholesterol Of 52 correlation coefficients 35 were based on 50 or more observations Nineteen of the 35 correlation coefficients were significantly different from zero Again most of the slopes were positive and the regressions essentially linear leading to the same conclusions which were drawn with regard to comparisons of cholesterol levels

There has of course never been any question that genetic factors are important in determining blood pressure and serum cholesterol levels a view also supported by several studies on twins The problem relates to the relative importance of genetic and environmental factors not only in the upper range but over the whole distribution of these variables There is no answer to this question at this time However there is at least some evidence that familial aggregations of coronary heart disease are in part conditioned by these two factors

With regard to blood pressure only the studies by Thomas and Cohen [1] already cited, provide relevant information in this connection When one or both parents (i e the parents of the medical students under study) were hypertensive the frequency of coronary disease in their siblings was 5 per cent a little but not significantly higher than the frequency of 4 2 per cent when both parents were normotensive Similarly the frequency of coronary disease in the offspring (sons and daughters combined) of the students grandparents was slightly but not significantly higher when one of the grandparents was hypertensive however the daughters of hypertensive parents had significantly more coronary disease than did those of normotensive parents In view of the diagnostic difficulties inherent in these data the somewhat surprising lack of a stronger effect may not be meaningful

With regard to serum cholesterol levels the evidence is somewhat more telling Thomas[31] again noted that no less than 9 per cent of 612 students had serum cholesterol levels of 300 mg per cent or over—a startling figure in itself Thirty two per cent of these students had a parent with coronary disease as opposed to 12 per cent of students with levels below 300 mg per cent It may be assumed that some of the parents of the hypercholesterolemic students were hypercholesterolemic themselves More recently Basset[32] studied 19 male medical students and one re

physician who had fathers with coronary disease and two groups of males who served as controls. The average cholesterol level in the subjects was 219 mg. per cent as compared with 181 and 193 mg. per cent, respectively, in the two control groups. Gofman's extensive data on 876 employed men 30 to 39 years of age point in the same direction.[32] Using the atherogenic index derived from ultracentrifugally determined beta-lipoprotein levels at different flotation rates, and setting at 1.0 the relative risk of having a father dead of heart disease when the atherogenic index was under 40 units, Gofman found that the relative risk increased steadily to a value of 4.87 when the index was 100 units or over. It is of interest that only 3 per cent of the men had indices under 40, whereas 46 per cent had indices over 60, at which point the relative risk had reached the level of 3.28.

B. Other mechanisms of genetic transmission. It is most likely that blood pressure and serum cholesterol are not the only factors which may predispose to aggregations of coronary disease in families. Gertler and White,[1] Pell and d'Alonzo,[34] and Bronte-Stewart[3, 35] have all studied the relation of blood groups to coronary disease. Only Bronte-Stewart and his colleagues found a significant relation, indicating a deficiency of blood group O in individuals among patients with coronary disease manifested as myocardial infarction but not among patients presenting with angina pectoris. Interestingly, this phenomenon was demonstrable only in the ethnic subdivisions which showed a relatively low prevalence of coronary heart disease. Bronte-Stewart believes that the genetic factor involved may be masked among populations with a high prevalence of disease since in them environmental factors such as diet could overshadow in importance the genetic element related to blood groups. Although the relationship between blood groups and coronary disease remains in doubt, such a masking effect might explain in part the negative results obtained in the other two studies.

Other hereditary traits might well enter into a predisposition to coronary atheroma. Thus Murphy and Mustard[37] found platelet survival and turnover shortened and in vitro clotting tests more active in persons with atherosclerotic disease or a history thereof than in controls. The anatomic configuration of the coronary tree, presumably an inherited trait, might influence the deposition of atheromata on account of the alterations in the dynamics of blood flow. Tissue repair responses to injury may also be under hereditary control. Body build and obesity, likewise influenced by heredity, are related to predispositions to coronary disease as may be certain emotional characteristics which could be to some extent at least inborn. There is clearly no end to the possibilities for idle speculation; the need is for factual information.

In view of the recent interest in the relation between elevated serum triglycerides and coronary disease, it is recalled that Hirschhorn[38] has found hyperlipemia to occur with a frequency of as much as 2 or 3 per cent among medical students. Although the relationship between triglyceride and cholesterol metabolism or their precise genetic determinants have not been established, these problems are of certain relevance to atherogenesis and its hereditary aspects.

In a discussion of the mechanisms of genetic transmission, the frequency of coronary disease in diabetic patients must arouse curiosity. It is rather strange how little work has been done on the simultaneous study of these two disorders in the same families and that reports from the major epidemiological studies of coronary heart disease have so far omitted data on the coexistence of these conditions. Bois[39] was surprised to find that the age of onset of coronary disease was the same in his diabetic and nondiabetic patients. He suggested that coronary disease might not be so much a consequence of diabetes but that both could be due to a similar underlying disturbance, manifesting in some as diabetes, in others as coronary disease. Conn and Fajans[40] suggested that the defect in protein synthesis in diabetic patients which might cause the elaboration of an abnormal insulin molecule could also be responsible for the structural faults in the vascular systems of these persons. As part of our epidemiological study of Italian and Jewish clothing workers in New York

some years ago[41] we attempted to collect some data on these interrelations[42] Family histories on siblings of 106 probands with diabetes and siblings of 224 probands with coronary heart disease were obtained Coronary disease was reported for 9 8 per cent of the 173 male and 4 9 per cent of the 144 female siblings of probands with diabetes the corresponding figures for the 318 male and 309 female siblings of probands with coronary heart disease were 21 1 and 10 0 per cent respectively Thus coronary heart disease was found more frequently among the siblings of probands with coronary heart disease than among the siblings of probands with diabetes Conversely diabetes was reported more frequently for siblings of diabetic probands than for siblings of probands with coronary disease 11 6 per cent of the male siblings and 12 5 per cent of the female siblings of diabetic probands also had diabetes whereas diabetes was reported for only 2 5 per cent of the male siblings and 3 9 per cent of the female siblings of probands with coronary disease Coexistent diabetes and coronary disease was reported for 2 3 per cent of the male siblings and 1 4 per cent of the female siblings of diabetic probands the corresponding figures for siblings of coronary disease probands were 2 5 and 1 3 per cent respectively Thus coronary disease was found more frequently among the siblings of probands with coronary disease than among the siblings of probands with diabetes conversely diabetes was found more often among the siblings of probands with diabetes than among the siblings of probands with coronary heart disease Calculations to demonstrate associations between coronary disease and diabetes showed no deviations from randomness i e there was no evidence for an association between these disorders These results were disappointing but it must be remembered that the data were all based on histories obtained from the proband It is quite possible that a person with a given disese is more apt to report the same disorder in a sibling than is a person who does not have the disease himself Many of the studies already discussed suffer from the same limitations We reviewed some years later the charts of all patients with diabetes who registered at the University Hospital in Ann Arbor between 1951 and 1956 and whose age at first registration was between 20 and 40 years[43] Thus the index cases were all diabetics whose disease started relatively early and who might be expected to show a stronger genetic component among their families than older diabetics Of 558 such patients 107 lived within a 30 mile radius of Ann Arbor Thirty-one of these patients were interviewed in regard to their family history whereas the history on the other 76 patients was obtained from their charts This review likewise failed to reveal any striking concentrations of coronary disease in parents and sibings of diabetics The actual rates for the occurrence of coronary disease in these parents and siblings of diabetics were strikingly similar to those reported by Thomas[15] who found coronary disease about 1 5 times as frequently in siblings of diabetics as in nondiabetics this difference was not statistically significant Evidence that coronary disease and diabetes might be different facets of a similar disturbance is therefore lacking but proof of such a relationship is so difficult to obtain and the hypothesis is so attractive that it should be pursued further

Methodological problems

The study of familial factors in health and disease hinges on a number of requirements It is necessary to obtain groups of patients and controls who are representative of the universe from which they are derived Data on a major proportion of the kindreds involved must be available The data must be accurate In situations in which familial aggregations are not striking the population studied must generally be large If after all these provisions have been fulfilled familial aggregations are found the relative importance of genetic and environmental factors must be evaluated In the case of coronary disease all of these requirements present methodological problems Most serious perhaps are the difficulties of diagnosis particularly of preclinical disease It is difficult enough to diagnose coronary disease on many occasions even when the subject is available for careful clinical examination but it seems more than risky to make the diagnosis in a relative deceased or

reach on hearsay evidence, yet this is what one is often forced to do in these studies.

Before we illustrate these problems by describing some of the results from an actual study, a brief look at the problems of general approach and numbers may be in order. Let us assume for the sake of simplicity that every middle-aged man in a representative American population has on an average one brother, so that the total population of middle-aged men would be represented by a large number of pairs of brothers. Let us take at random 1,000 such pairs and postulate, in fair agreement with observation, that the prevalence of coronary heart disease in such a population is 5.5 per cent. Among the 2,000 brothers in this population there will be 110 cases of coronary disease, 55 occurring in the first and 55 in the second member of the pair. On the basis of chance alone, 6 of these cases will occur in 3 brother pairs (0.0055 times 0.0055 equals .00302); the other 104 cases will be singletons. If there were familial aggregations of coronary disease equal to 2 or 4 times random expectation, 6 or 12 brother pairs, respectively, would be affected simultaneously. It is noteworthy that even with a risk 4 times greater than chance, familial aggregations, as it were, will be observable in only 12 out of 1,000 sibships.

These findings may be considered either from the "index case-control" or "population genetics" point of view. Of the two, the index case-control approach is more commonly employed and in some ways is more easily accomplished in practice. In the situation in which familial aggregations are 4 times greater than chance it will show that the prevalence in sibs of propositi is 22 per cent (12/55), in sibs of controls 4.6 per cent [(55 − 12) / (1,000 − 55)], indicating that the disease is 4.8 times as common in sibs of index cases as in controls. The disadvantage of this approach is its failure in general to reveal the proportion of cases in a population which are in fact familial. Therefore, in the situation in which a total population is studied, one will obtain the additional data that, in the same example, 22 per cent of the cases (24/110) were familial. Up to this point the information is of course purely statistical, and further data are needed to indicate the genetic and environmental attributes which cause these aggregations. It is of interest that these calculations based on this useful model are highly influenced by prevalence rates. A prevalence rate of 5.5 per cent for coronary disease reflects, of course, no more than the "top of the iceberg," an additional number of cases being hidden beneath the surface on account of the relative insensitivity of diagnostic instruments. With a prevalence rate of 20 per cent, which is closer to the objective picture as a pathologist would see it, the corresponding calculations would show a sixteen-fold differential for the index case-control approach and no less than 80 per cent of familial aggregation, assuming again a concordance rate of affected sibs 4 times greater than chance. The argument will not be pursued beyond this point, but may help to illustrate the complexities of the issues at stake and the need for studies to test the actual facts against these population models.

In our own prospective studies in the town of Tecumseh, Michigan,[41,44] we have an opportunity to carry out one such test among a series of other integrated activities.* Of the 9,600 inhabitants of this town approximately 90 per cent have been examined once. The preliminary data to be reported are based on these examinations. More reliable information will emerge with each subsequent round of re-examinations. During the first round, 248 persons with clinically manifest coronary heart disease were identified, using criteria serving the needs of this particular analysis. These belonged to 242 sibships, since there were 6 sibships with multiple cases. The sibships comprised 1,213 men and women. About a quarter of these were examined, and about another quarter were deceased. A third of the sibs lived beyond immediate reach, but about 1 in 8 lived sufficiently close to the study area to be interviewed; the latter persons have not yet received a physical examination. This is one of the hazards of doing such studies in the United

*These investigations were conducted in collaboration with the Research Staff of the Tecumseh Community Health Study, Cardiovascular Research Center, University of Michigan, supported by Program Project Grant H 6378 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

States where the population is relatively mobile. It is left open to question whether living within the study area or farther away is related to the disease under investigation and might thus introduce a bias. In this essentially total community comprising, in addition to younger people, 2,214 men and women who were 40 years of age and over, there were 6 sibships, as already mentioned, in which there was more than a single case of coronary heart disease among the members examined. In one of these, in addition to the 2 index cases, a sister died of a heart attack at the age of 52, and in another, 2 additional brothers and a sister were interviewed and one of the interviewed brothers had suspect coronary disease. These pedigrees illustrate the kind of data obtainable in a large epidemiological study of this type. The multiple cases in 2 of these 6 sibships are half brothers and half sisters.

In addition to these 6 sibships, there were 10 other sibships in which there was one examined person with coronary disease and one *interviewed* sibling who gave a history of myocardial infarction or angina pectoris; in one of these 10 sibships, 2 additional brothers died of "heart trouble." Another category includes 43 sibships in which, in addition to the examined index case, a brother or sister had died of a "heart attack" or "heart trouble"; these sibships included no interviewed sibling who reported evidence of coronary disease. There remained 183 sibships comprising 843 persons in which the index case was the only known instance of "probable" coronary heart disease in the sibship and in which no person was reported to have died of this disease. In these sibships, of course, as well as in the others, new events of coronary heart disease will occur as time progresses.

Disregarding for the time being the problems of diagnostic identification already mentioned, it may now be asked whether the familial data just described indicate that coronary heart disease aggregates in these sibships more often than expected by chance. The answer to this question involves comparison with control kindreds or calculation of expected versus observed frequencies, utilizing the data from the total population as discussed elsewhere.[24] This intricate analysis has not yet been completed. In the meantime, it would seem fair to state that a clinical rather than statistical look at these data fails to indicate a striking degree of familial concentration of cases on the basis of a one-time cross-sectional survey. This is similar to the situation observed in other chronic diseases. This may be due, in part, to the fact that in conditions which are influenced by multiple genes a large part of the variation between individuals is concealed[43]; on the other hand, even slight differences in disease frequency between relatives of probands and controls may be very meaningful.[44] Thus, it cannot be concluded in any way that familial factors are of relatively minor importance in the genesis of coronary heart disease. It seems more likely that the error lies in using as an index of genetic predisposition the end result, i.e., clinically manifest disease, rather than the underlying biologic disturbances in terms of metabolic or other defects. If one could identify and measure all of these predisposing traits, it would probably emerge that they are even more widespread than the prevalence of the disease would suggest and show more clear-cut distributions within kindreds. Prevention of coronary heart disease demands that the carriers of these traits be identified so that prophylactic measures can be instituted at an early age among genetically susceptible individuals. Although there is undoubtedly very much more to be learned about these traits, the association between coronary disease and elevated levels of serum cholesterol and blood pressure makes it likely that the determinants of these particular two variables are, for lack of a better term, an integral part of an "atherosclerotic constitution." In fact, the data from the Tecumseh Study indicate that elevation of one or both of these variables (serum cholesterol 260 mg. per cent or above and/or blood pressure 160 mm. Hg systolic and/or 96 *mm. Hg diastolic* or above) occurred among 7 of the 12 index cases in the 6 sibships in which there was more than one affected and examined individual. Moreover, in 5 of these 6 sibships there was at least one person with at least one of these two variables in the elevated range. In sibships with one examined and one interviewed person with coronary disease, 7 of the 10 index cases showed elevation of one

or both of these variables. Altogether rather more than one half of the persons with coronary heart disease, regardless of age and sex, showed serum cholesterol or blood pressure levels in a range in which genetic influences almost certainly play an appreciable role. These figures may be compared with an over-all prevalence rate of 24 per cent for cholesterol and/or blood pressure elevations in the total Tecumseh population, including the persons with coronary disease, between ages 40 and 69.

Evolution and natural selection

In the foregoing discussion, an attempt was made to show that the exact mechanisms and role of heredity in the development of coronary heart disease remain to be established. At the same time, the evidence certainly favors the belief that genetic factors are involved in the pathogenesis of the atherosclerotic disorders. Assuming the existence of such factors, we may ask whether the striking differences in the frequency of coronary heart disease among different population groups may have, in part, a genetic basis. Are some of the genes predisposing toward atherosclerosis more frequent, say, in the United States than in the Netherlands or Japan? There is clearly no definitive answer to this question at the present time, although there is some circumstantial evidence that these particular differences may be related more to environmental than genetic variations. Even in our study among Italian and Jewish clothing workers in New York City,[41] specifically designed to answer some of these questions, we hesitated to ascribe the higher prevalence of coronary disease among the Jewish men necessarily to genetic factors, since there were potential environmental differences, such as early rather than current dietary habits and others, which remained under suspicion.

Regardless of the reasons for the geographic and ethnic differences mentioned, the fact remains that coronary disease is highly prevalent in some populations. If hereditary factors contribute significantly to this situation, it must follow that the responsible genes must also occur with considerable frequency. At least two factors may have contributed to this situation which causes concern from a biologic point of view, unless one holds the cynical attitude that this state of affairs helps to eliminate older people who tend to be a burden on the young and vigorous. Firstly, if a disease is partly determined by heredity and if age of onset is also under hereditary influences, natural selection will gradually determine that it will occur more and more in the postreproductive period[42]—the time at which coronary disease actually becomes manifest most commonly. Secondly, it has been suggested that the genes predisposing to atherosclerosis may have a selective advantage, for instance in times of famine,[43,44] when the carriers of these traits might withstand the hazards of starvation by being able to store fat more effectively in their depots and, alas, their arteries.

Thus, natural selection could cause accumulation of these genes in the population. Could natural selection also have the reverse effect and help in eliminating these genes? Lown and Stare[45] have stated that diseases such as atherosclerosis have not been culled from the stream of inheritance by rigorous evolutionary process since natural selection cannot operate beyond the phase of reproduction. Although this is true in the strict sense, it is entirely conceivable that the carriers of these genes might be less fertile or show a higher mortality in the prereproductive or reproductive periods. Even small fertility or mortality differentials over the generations may have a profound effect on gene frequencies.[46] The factors involved in causing fertility or mortality differentials may be affected by both biologic and sociocultural influences. Genetic and environmental interactions which determine selective pressures are well recognized.[47,48] Without speculating on possible mechanism, it is merely stated that the diseases which present past the reproductive period are not necessarily removed from the forces of natural selection, and that potentially selective influences are not entirely powerless to counteract the accumulation of the responsible genes.

Even if there were an inexorable tendency for these genes to become more frequent, it would not necessarily follow, as McKeown[49] has proposed, that only selective breeding is likely to result in a profound change in the causes and extent of

mortality in the postreproductive period. If the genes which predispose toward atherosclerosis are sensitive to environmental influences, their expression might be appreciably suppressed by changes in the mode of life. The need therefore would be to detect the carriers of these traits early in life so that preventive measures might be instituted among susceptible persons in order to forestall the development of pathologic changes.

Summary

Currently available data on aggregations of coronary heart disease among relatives have been reviewed, and the interrelationships between genetic and environmental factors responsible for familial predispositions toward coronary atherosclerosis have been discussed. Although the evidence suggests a definite but not striking tendency for coronary disease to cluster in families, a quantitative assessment of the relative importance of familial influences in the genesis of these disorders is not possible at the present time. The first step toward the solution of the methodological problems involved lies in the recognition of their nature. It is suggested that the true extent of familial aggregations of coronary heart disease can only be estimated with assurance on the basis of long-term, rather than one-time, studies of families representative of the population at large.

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Coronary flow measured by the nitrous-oxide method

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The nitrous-oxide method for measuring cerebral blood flow was first reported as adapted for determination of coronary blood flow in experimental animals in 1947[1] It was applied to man very shortly thereafter[2] and a considerable body of information has accumulated from its use Periodically it seems to be worth while to evaluate continuing experience with a method especially as data accumulate relative to its reliability The present paper is devoted to such a purpose and will consist of an attempt to answer a series of questions considered pertinent to the method

Does the procedure used for determination of coronary flow alter hemodynamics?

Although it is implicit in the nitrous oxide method that a concentration of 15 per cent nitrous oxide does not alter hemodynamics significantly we have been able to find no specific references to data concerning this point We believe that there probably are such data but since they are not readily available it would seem that they should be presented

In Fig 1 can be seen the effect of administering a gas mixture of 21 per cent oxygen 15 per cent nitrous oxide and 64 per cent nitrogen to an experimental animal during continuous measurement of coronary blood flow with a rotameter The rotameter was attached in the traditional fashion between the internal carotid artery and the circumflex coronary artery of a heparinized dog When coronary flow was stable as determined by the rotameter the gas mixture was introduced into the respirator which maintained pulmonary ventilation so that the nitrous oxide was administered in a manner similar to that in which it is used for determination of coronary blood flow The mixture was alternately administered and withdrawn on several occasions and the results were consistently similar to what is shown in Fig 1 It can be seen that there was no measurable effect of the nitrous oxide on coronary blood flow †

It should also be established whether the procedure as a whole alters systemic hemodynamics This possibility was investigated

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when neither blood was being withdrawn nor pressures measured and it was estimated that during the procedure the volume of blood removed was replaced by an equivalent volume of saline solution

The data from this study are presented in Fig 2 In this study the cardiac output calculated by the Fick principle averaged 3 0 liters per minute whereas that determined by the dye method averaged 2 9 liters per minute with an r value for correlation of +0 83 ($p<0\,001$) This seems to be satisfactory when it is considered that Fick cardiac output was determined over 5 minutes and that by the dye method over approximately 30 seconds The rest of the data in Fig 2 compare the hemodynamics as measured by the indicator-dilution method first during the determination of cardiac output by the Fick principle and second during the determination of coronary blood flow by the nitrous-oxide method A comparison of these two sets of data showed no significant change in cardiac output or heart rate and hence stroke volume was the same Although there was a tendency for blood pressure to decline in the systemic and pulmonary arteries as well as the right atrium and for right and left ventricular work to decrease none of these changes were significant Peripheral vascular resistance tended to rise slightly whereas pulmonary vascular resistance was unchanged Neither the hemoglobin nor hematocrit decreased significantly

In summary even with the unavoidable deliberate and accidental loss of blood incurred during this procedure the vagaries of anesthesia the manipulation of catheterization and the administration of a foreign gas no hemodynamically or statistically significant changes occurred in the systemic pulmonary or coronary circulation

Does the nitrous oxide method measure the same quantity when it is repeated or when an inactive substance is administered?

Data from our laboratory for a control group of 10 dogs administered morphine–Dial urethane anesthesia as described in the preceding section were mentioned[3] but not published previously In this study cardiac output and coronary blood flow were determined by the Fick principle and nitrous-oxide method respectively at an interval of approximately 20 to 35 minutes The data from this study are summarized in Table I It will be observed that with this particular anesthetic mixture as indicated

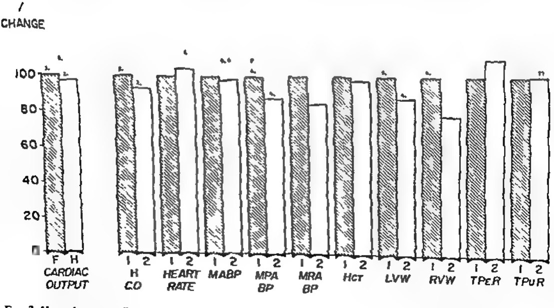

Fig 2 Hemodynamic effect of the nitrous-oxide method F Fick principle H Hamilton method 1 During determination of cardiac output by the Fick principle 2 During determination of coronary blood flow by the nitrous-oxide method

Table I. Control series for hemodynamic studies of cardiac output and coronary blood flow (10 dogs; morphine-Dial-urethane anesthesia)

Factor	Control	After saline	Per cent change
Heart rate (beats/minute)	87 ± 17	95 ± 14	+9.2
Mean femoral blood pressure (mm. Hg)	116 ± 17	112 ± 16	−3.4
Mean pulmonary arterial blood pressure (mm. Hg)	13 ± 3	14 ± 2	+7.7
Oxygen consumption (ml./minute)	108 ± 25	112 ± 20	+3.7
Respiratory quotient	0.89 ± 0.04	0.91 ± 0.07	+2.2
Cardiac output (L./minute)	2.3 ± 0.8	2.7 ± 0.6	+17.4
Coronary blood flow (ml./100 Gm./min.)	90 ± 16	87 ± 17	−3.3
Coronary vascular resistance (units)	1.3 ± 0.4	1.3 ± 0.3	0
Coronary sinus oxygen (ml./100 ml. of blood)	4.1 ± 1.8	4.7 ± 1.3	+14.6
Cardiac metabolic rate—O_2 (ml./100 Gm./minute)	10.9 ± 1.9	11.1 ± 2.3	+1.8
Cardiac respiratory quotient	0.88 ± 0.04	0.87 ± 0.02	−1.1
Index of efficiency (LVW ÷ CMRO$_2$)	0.35 ± 0.14	0.38 ± 0.11	+8.6

Table II. Control series for hexamethonium studies of cardiac output and coronary blood flow (15 Dogs; morphine-pentobarbital anesthesia)

Factor	Per cent change from first to second study
Mean arterial blood pressure (mm. Hg)	+3
Coronary flow (c.c./100 Gm./min.)	−8
Cardiac O_2 consumption (c.c./100 Gm./min.)	+4
Cardiac output (L./minute)	−9
Cardiac work (Kg. M./minute)	−6
Cardiac rate (per minute)	−3
Calculated T.P.R. (MU)	+10
Arterial-coronary sinus O_2 difference (vols. %)	+13*
Coronary sinus O_2 (vols. %)	−14

*Statistically significant, $p < 0.05$.

by others,[4] a prolonged stable state of anesthesia is secured during which reliable data can be collected concerning cardiac output and coronary blood flow. Similar data (Table II) collected in 15 dogs during anesthesia with morphine and pentobarbital indicated that during the first and second determinations of cardiac output and coronary blood flow there was a relatively stable state.[5] However, a significant decrease occurred in coronary sinus oxygen content with an increase in the arterial-coronary sinus oxygen difference. Furthermore, there tended to be progressively lighter anesthesia of somewhat less stability. Used as the sole anesthetic agent, pentobarbital produces tachycardia and a high output state with a considerable increase in coronary flow. Consequently, it has been the custom in our laboratory in recent years to use the longer-acting morphine-Dial-urethane anesthetic.

As a part of observations on systemic and coronary hemodynamics of the normal human male and female,[6] cardiac output and coronary blood flow were determined in duplicate in 13 consecutive normal women. A cardiac catheter was introduced into the pulmonary artery and a needle placed percutaneously in the femoral artery for determination of cardiac output by the Fick principle. After the original determination of cardiac output, the catheter was withdrawn from the pulmonary artery and placed in the coronary sinus for measurement of coronary blood flow. Subsequent to determination of coronary blood flow, the subjects rested quietly on the catheterization table for a period of 20 to 30 minutes, at the end of which time the coronary blood flow was measured again. The catheter was then withdrawn from the coronary sinus and replaced in the pulmonary artery for the second determination of cardiac output. The essential data derived from this study are presented in Table III. It is apparent that these normal subjects without anesthesia or premedication of any kind were not in a completely stable state. The slight but significant in-

crease in oxygen consumption and the decreases in pulmonary arterial pressure and right ventricular work should be noted as should the relative stability of cardiac output coronary blood flow cardiac oxygen consumption and cardiac efficiency

Two additional sets of double-control observations in man are available One of these served as the control for a study of the hemodynamics of hydrazinophthalazine [7] and the other is the control for the effect of hypotension due to spinal anesthesia on coronary blood flow and myocardial metabolism [8] The more pertinent data from the tables in these two articles are summarized and presented in Table IV It is apparent that in these abnormal human subjects the hemodynamic state

Table III Duplicate observations of cardiac output and coronary blood flow in normal human female subjects

Factor	*Before*	*After*	*Per cent change*	*p value <*
Heart rate (beats/min)	83	80	−3.6	0.1
Mean arterial blood pressure (mm Hg)	90	93	+3.3	0.2
Mean pulmonary arterial blood pressure (mm Hg)	17	15	−11.8	0.01
Oxygen consumption (ml /min /M²)	178	136	+5.7	0.05
Respiratory quotient	83	78	−6.0	0.1
Arteriovenous O_2 difference (ml /100 ml of blood)	3.3	3.7	+12.1	0.01
Arterial-coronary sinus O_2 difference (ml /100 ml of blood)	10.8	11.1	+2.8	0.2
Coronary sinus O_2 content (ml /100 ml of blood)	5.2	5.0	−3.8	0.5
Arterial hematocrit (%)	41	41	0.0	[illegible]
Cardiac index (L /min /M²)	4.0	3.7	−7.5	0.2
Total peripheral resistance (c g s units)	1 138	1 272	+11.8	0.1
Total pulmonary resistance (c g s units)	220	201	−8.6	0.4
Left ventricular work index (Kg M /min /M²)	4.9	4.7	−4.1	0.4
Right ventricular work index (Kg M /min /M²)	1.0	0.8	−20.0	0.001
Coronary blood flow (ml /100 Gm /min)	96	94	−2.1	0.7
Cardiac metabolic rate—O_2 (ml /100 Gm /min)	10.3	10.4	+1.0	0.9
Coronary vascular resistance (units)	98	1.06	+8.2	0.7
Cardiac respiratory quotient	0.77	0.72	−6.5	0.05
Index of efficiency (LVW ÷ $CMRO_2$)	0.48	0.47	−2.1	0.8

Table IV Control observations on the hemodynamics of abnormal human subjects

Factor	*6 Patients with various diseases (Hackel et al)*			*5 Patients with hypertension (Rowe et al)*			*Total average difference (%)*
	First	*Second*	*Per cent change*	*First*	*Second*	*Per cent change*	
Heart rate (beats/minute)	70	66	−5.7	80	79	−1	−3.5
Mean arterial blood pressure (mm Hg)	90	90	—	140	147	+5	−2.8
Cardiac index (L./min /M²)	—	—	—	3.0	[illegible].7	−10	−10
Coronary blood flow	87	80	−2.5	67	67	—	−1.1
Coronary sinus O_2 content (ml /100 ml /min)	4.8	4.8	—	6.8	6.8	—	
Δ Arterial-coronary sinus O_2 (ml /100 ml /min)	8.6	8.5	−1.1	12.1	12.0	—	
Left ventricular O_2 usage (ml /100 Gm /min)	9.6	9.4	−[illegible].1	8.0	8		

Table V Systemic and hemodynamic effects of Premarin

Factor	Before	After	Per cent change
Heart rate (beats minute)	83	84	+1 2
Mean systemic arterial blood pressure (mm Hg)	114	118	+3 5
Mean pulmonary arterial blood pressure (mm Hg)	17	17	—
Mean coronary sinus blood pressure (mm Hg)	4 8	4 7	−2 1
Cardiac index (L /min /M²)	3 4	3 9	+14 7
Coronary blood flow (ml /100 Gm /min)	80	79	−1 3
Cardiac metabolic rate—O_2 (ml /100 Gm /min)	9 7	9 7	—
Coronary vascular resistance (units)	1 29	1 28	−0 8
Index of efficiency (LVW ÷ CMPO)	0 50	0 56	+12

remained relatively stable for a period of time sufficient for the accomplishment of a control and experimental study

Similar information as to the stability of human subjects during the determination of cardiac output and coronary blood flow may be obtained from data concerning the hemodynamic effects of intravenous administration of Premarin In these subjects cardiac output was determined by the Fick principle and coronary blood flow by the nitrous oxide method before and 1 hour after the intravenous administration of 20 mg of Premarin It will be seen by examining the data in Table V that in these human subjects no marked hemodynamic changes occurred subsequent to the administration of this estrogenic substance and again the stability of this type of study is indicated A more rigorous test of rapport between patient and investigator was that in which coronary and systemic hemodynamics were measured in a group of subjects with angina pectoris before and after ligation of the internal mammary artery under local anesthesia [9] No significant hemodynamic changes occurred

Coronary blood flow for normal subjects as determined in many different laboratories is presented in Table VI [6 10 16] It is immediately apparent from a survey of the data from widely separated centers in the United States Europe and the Orient that values for coronary blood flow coronary sinus oxygen content arteriovenous coronary sinus oxygen difference and left ventricular oxygen usage are acceptably constant Thus in the experience of investigators under greatly different circumstances the method tends to give the same results For whatever it may signify these results are very similar on unit weight basis to those results which have been reported in the dog after large numbers of observations utilizing the rotameter [17]

In summary although neither the data from experimental animals nor those from human subjects show complete hemodynamic stability the range of variation is not excessive and statistical testing which must always be done in the presence of such variability tends to correct differences related to random variation

Does the nitrous oxide method measure coronary blood flow?

The only data concerning the accuracy of the nitrous oxide method are contained in studies in which this method was compared with the bubble flowmeter[18] and with the rotameter [19] In both of these studies a relatively good degree of correlation was established and in the comparison of coronary flow as measured by the nitrous oxide method and that by the rotameter the average variation between the two methods was ±12 4 per cent [19] It is conceded that the spread above and below the flow measured by relatively exact methods is more than is desirable However it is apparent that the circumstances under which the nitrous oxide method was tested were not ideal since it is most useful in the intact specimen whereas both the bubble flowmeter and the rotameter re

quire considerable dissection for their application. When the heart is exposed there is evidence that nitrous oxide diffuses from its surface, which tends to produce errors in the estimates of myocardial nitrous-oxide uptake so that care must be taken to avoid this error.[19] In the intact animal with all tissues about the heart receiving a similar concentration of nitrous oxide there is less reason to expect this loss to occur. We do not mean to imply any criticism of these careful and fundamental studies of standardization of the nitrous oxide method but intend only to emphasize that the inert gas method may have been at a disadvantage under the circumstances required in the experimental situation. Even if the variation demonstrated by these studies is accepted, it would seem that considerable confidence can be placed in results obtained by the nitrous-oxide method provided that a significant series is investigated and statistical tests are used.

Does the nitrous oxide method measure a change in coronary blood flow under circumstances in which a change is expected and does the change go in the predicted direction?

It is accepted by most investigators that adenosine triphosphate (A.T.P.) is an exceedingly vasoactive substance when administered intravascularly in sufficient concentration.[20] Determination of coronary blood flow by the rotameter has indicated that a marked increase in coronary blood flow may be expected with the administration of A.T.P. A summary of the systemic and coronary hemodynamic data obtained by the Fick principle and the nitrous-oxide method during continuous infusion of A.T.P. into the right atrium of anesthetized mongrel dogs is seen in Table VII. It is apparent that this compound is vasoactive in the intact animal when administered systemically.

Similar data for a vasoactive drug in human beings may be found in the hemodynamic effects of hydralazine.[7] This agent has been shown to be effective in increasing cardiac output, renal blood flow, cerebral blood flow, and coronary blood flow. The data are sufficiently internally consistent to suggest that the agent is a generalized vasodilator and this thesis fits with the clinical observations of flushing, vascular headache, palpitation, and tachycardia in subjects receiving this agent. Data concerning the ganglion blocking drugs are equally internally consistent, indicating that cardiac output decreases accompanied by a decrease in coronary blood flow, reduced left ventricular work, and decreased left ventricular oxygen consumption.[4]

Data from chronic abnormal states indicate that in subjects with mitral stenosis cardiac output is reduced, left ventricular work is decreased, and coronary blood flow is decreased. Furthermore, the decrease in coronary blood flow is greater in those

Table VI. Normal values for coronary blood flow (correct to partition coefficient of 1 for uniformity)

	Number of subjects	Coronary blood flow*	Coronary sinus O_2†	A-V arterial-coronary sinus O_2†	Left ventricular O_2 usage
Bing	18	77		12	9.4
Goodale et al	5	86			
Calazel et al	8	78	4.9	17.2	9.2
Kobayashi et al	15	69		10.5	7.1
Leight et al	8	93		10.3	9.5
Rowe et al	30	85	5.7	11.6	9.7
Regan et al	9	74		10.4	8.5
Brachfeld et al	10	66	5.3	12.5	8.3
Average or total	103	79	5.5	11.4	8.9

*Milliliters per 100 Gm. per minute.
†Milliliters per 100 ml. of blood.

Table VII. Systemic and coronary hemodynamic effects of A.T.P.

Factor	*Control*	*Study*	*Per cent change*	*p Value <*
Heart rate (beats/minute)	76	131	+72.4	0.001
Mean arterial blood pressure (mm. Hg)	116	100	−13.8	0.001
Oxygen consumption (ml./minute)	104	105	+1.0	0.4
Cardiac output (L./minute)	2.4	3.3	+37.5	0.01
Left ventricular work (Kg. M./minute)	3.9	4.4	+15.4	0.2
Total peripheral resistance (c.g.s. units)	4,032	2,549	−37.1	0.01
Coronary blood flow (ml./100 Gm./min.)	73	464	+534.2	0.001
Δ Arterial-coronary sinus O_2 (ml./100 ml.)	11.5	3.2	−73.0	0.001
Coronary sinus O_2 (ml./100 ml.)	5.5	15.0	+172.9	0.001
Coronary vascular resistance (units)	1.69	0.27	−84.0	0.001
Cardiac metabolic rate—O_2 (c.c./100 Gm./min.)	8.3	12.3	+48.2	0.01
Index of efficiency (LVW ÷ CMRO$_2$)	0.47	0.37	−21.3	0.05

subjects with mitral stenosis who are clinically further along in the course of their disease and have chronic atrial fibrillation.[20] Similarly, studies in subjects with thyrotoxicosis have revealed an increase in cardiac output and coronary blood flow during the thyrotoxic state; these return to normal subsequent to effective therapy for this disease.[3] Data from subjects with polycythemia rubra vera with elevated blood oxygen carrying capacity and increased blood viscosity have revealed slowing of coronary blood flow.[24] In anemic[5] and hypoxic[6] human subjects coronary flow is increased, but with correction of the anemia and hypoxia the coronary flow returns toward normal. Cardiac output and coronary blood flow have been seen to increase with exercise,[7] as has been shown to occur in dogs[8] and as would be expected from teleological reasoning.

In summary, the nitrous oxide method has revealed coronary flow to be increased in those circumstances in which we know from ancillary evidence that it should be increased. Similarly, in most situations in which it seems that coronary flow should be decreased, the nitrous oxide method has confirmed that it is reduced.

How predictably can the coronary sinus be catheterized?

In many discussions of the nitrous-oxide method for determination of coronary blood flow the impression has been given that intubation of the coronary sinus is difficult and unpredictable. Indeed, anatomic evidence has been cited to indicate that the coronary sinus cannot be intubated in a significant percentage of subjects.[22] It is true that in very large hearts decreased visibility in the region of the coronary sinus behind the large mass of blood and muscle and over the vertebral column tends to be troublesome, but this difficulty has been largely eliminated by the use of electronic intensifiers. Furthermore, anatomic evidence indicates that the coronary sinus is enlarged in subjects with chronic failure[23] and thus lessens the difficulty. Indeed, in diagnostic cardiac catheterization, when intubation of the coronary sinus is undesirable, the impression is gained periodically that little other than the coronary sinus can be entered. Excessive irritability of the right atrium or tricuspid valve area of the right ventricle is a disturbing but infrequent problem.

Figures on the percentage of successes in deliberate attempts to measure coronary blood flow in human subjects do not seem to be available; therefore, the data books covering our entire experience with the nitrous oxide method in man have been surveyed in an attempt to obtain figures for our laboratory. Although we cannot state for certain that no studies were missed, we did make a concerted effort to review every attempt to measure coronary blood flow during this period. Of 256 consecutive recorded attempts to determine coronary flow, excluding second measurements at the same catheterization but including first attempts on repeat catheterization on another day, there were 30

or 11.7 per cent failures. The causes of failure may be seen in Table VIII. In 10 cases (3.9 per cent) failure occurred because the catheter was not in the coronary sinus. In 6 of these (2.3 per cent) the catheter was thought to be in this proper position but either it was not or it became dislocated before the study was completed. In 4 instances (1.6 per cent) the investigators did not think that the coronary sinus had been entered at any time. Eight trials (3.1 per cent) are listed as technical failures attributable to human failure of some member of the team; examples of this type of difficulty are utilization of the wrong gas mixture, failure to clear the catheter system which results in clotting of the catheter, and breaks in continuity of administration of nitrous oxide. In 7 cases (2.7 per cent) for one reason or another the nitrous-oxide curves were unsatisfactory and could not be used. Miscellaneous causes of failure are listed in the table and constituted 2.0 per cent. The failures then in two out of three cases are related to some factor other than difficulty in catheterization of the coronary sinus. In consideration of the number of opportunities for error and the number of individuals in the team who are presented with that opportunity these results seem acceptable.

Table VIII. *Total experience concerning coronary blood flow method in man*

Measurement of coronary blood flow	*Number of times*	*Per cent*
Attempted	256	100.0
Succeeded	226	88.3
Failed	30	11.7
Reasons for failure		
Technical failure due to personnel	8	3.1
Unsatisfactory N_2O curves	7	2.7
Catheter not in coronary sinus during measurement	6	2.3 } 3.9
Unable to enter coronary sinus	4	1.6 }
Miscellaneous (each one case: shock, fever, atrial fibrillation, ventricular premature beats, patient would not tolerate mask)	5	2.0

In dogs whose body weight exceeds 17 or 18 kilograms deliberate intubation of the coronary sinus is routine and in our experience cannulation of the pulmonary artery, coronary sinus, and the right atrium utilizing three catheters can be accomplished with rare exception. The coronary sinus can usually be cannulated also in smaller dogs; however, frequently it is difficult to withdraw blood from the coronary sinus sufficiently rapidly or smoothly and the amount of blood withdrawn is so much greater percentagewise as to contraindicate their use for this purpose.

What are the disadvantages of the method? Many disadvantages are inherent in the nitrous-oxide method. Since the method requires cardiac catheterization, its use must be limited to those centers in which cardiac catheterization is available and in which there are sufficient trained personnel to carry out the test efficiently. Radiation exposure is a continuing hazard both to experimental subjects and investigators. Apprehension is natural in association with cardiac catheterization and may well distort the results particularly if care is not taken to insure that the experimental subject has confidence in the investigators. A certain amount of risk is inherent in the method, although reports of serious accidents during determination of coronary flow have not been found in the literature and such accidents have not occurred in our experience. The discontinuous nature of the determination of coronary blood flow and the limited number of times the study can be repeated in a single subject in a single day are considerable disadvantages, as is the fact that the results are not known until some time after the procedure has been completed. Hence an irregular or unpredicted result must be evaluated in retrospect. It is inconvenient that a steady state of several minutes duration is required for determination of coronary blood flow and even longer if systemic hemodynamic observations are included. This required prolonged steady state makes the method completely unsatisfactory for evaluation of transient events. Although repeated studies can be made in the same individual on different occasions, the distinct tendency for thrombophlebitis to occur in a vein which has been used f

cardiac catheterization eventually results in a practical limit to the number of times the procedure can be repeated It is desirable to use two cardiac catheters in subjects in whom immediately consecutive determinations of cardiac output and coronary blood flow are desired so that one catheter may be placed in the pulmonary artery and the other in the coronary sinus thereby eliminating the need for fluoroscopy and repositioning of the catheter in the middle of a set of observations This requires either a vein of considerable size or more suitably two veins sufficiently close together so that they may be exposed through a single incision or penetrated by two needles in the same surgical field

As this rather formidable list of disadvantages is surveyed it becomes apparent that with sufficient experience and motivation they are reduced chiefly to items of nuisance value which can be overcome provided that suitable projects are selected

Does the nitrous oxide method supply information worth having or does it merely reproduce results which are attainable by standard experimental tests in nonintact animal preparations?

As the result of studies in nonintact animal preparations it has been known for many years that nitrites dilate the coronary vessels and increase coronary blood flow [39] Data acquired by the nitrous-oxide method however indicate that whereas coronary blood flow increases in normal human subjects subsequent to the administration of sublingual nitroglycerin [16] it does not increase in those subjects with angina pectoris [17] Furthermore study of longer acting nitrites[4] has indicated that although coronary vascular resistance decreases subsequent to the sublingual administration of erythrol tetranitrate mean systemic arterial blood pressure decreases simultaneously and hence coronary blood flow does not change As with the shorter acting nitrites cardiac work decreases Both of these studies in human subjects indicate that effective therapy of anginal pain with nitrites is probably not due to an increase in coronary blood flow as had been assumed from the action of these agents in nonintact experimental animals but is apparently due to decreased cardiac work.

Another example of the manner in which the clinician is misled by data derived from the nonintact animal preparation is the repeated demonstration of increased coronary blood flow subsequent to the administration of aminophylline [30] Data accumulated by the nitrous-oxide method both in dogs[3] and in man[31] indicate that the systemic administration of this agent is not associated with an increase in coronary blood flow but is accompanied by a decrease in left ventricular work [31] and a decrease in coronary sinus oxygen content [31] Indeed it appears from the data accumulated in intact preparations that the myocardial oxygen tension is probably lower after the administration of aminophylline and it may well be concluded that the agent is contraindicated in subjects with ischemic myocardial disease

It cannot be emphasized too strongly that the administration of a pharmacologically active compound into the coronary circulation of an experimental animal bears no predictable relation to the systemic administration of the same agent in an intact animal or in unanesthetized man

Conclusions

1 Evidence is presented which indicates that the procedure of determining coronary blood flow by the nitrous-oxide method does not alter significantly the hemodynamic parameters which it purports to study

2 The method has given reproducible data in normal dogs as well as in normal and abnormal human subjects Furthermore results in widely separated laboratories are substantially the same

3 When compared with the bubble flowmeter and the rotameter the method has given an acceptable degree of correlation indicating that it does measure coronary blood flow

4 The fact that coronary blood flow as determined by the nitrous-oxide method changes in a predictable direction in response to pharmacologic agents as well as to physiologic and pathologic states supports its validity

5 In experienced hands the technique can be undertaken with considerable assurance of success in each subject and with undoubted success if a sufficient number of subjects are available

6 The disadvantages although numerous can be overcome to some extent by experience and careful selection of suitable subjects and projects

7 The data supplied by the method are sufficiently enlightening to make it invaluable in the study of the intact subject

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Glycogen-storage disease of the heart

Hemodynamic and angiocardiographic features in 2 cases

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Among the several varieties of glycogen storage disease, one stands out as an entity in which striated muscle, both cardiac and skeletal, is involved diffusely. This condition is commonly known as glycogen storage disease of the heart (or myocardium) or cardiac glycogenosis.

Glycogen storage disease involving the heart and skeletal muscles was described by Pompe[1,2] in 1932 and is commonly called by his name, although Putschar[3] and Bischoff[4] also reported this entity at the same time. More recently, Stetten and Stetten[5] have included this form as Type II in their biochemical classification of the glycogenoses.

Although glycogen storage disease of the myocardium is a rare form of cardiac disease, this condition has been reported with increasing frequency.[6-16] The salient clinical and pathologic findings are described in the articles quoted, along with extensive reviews of the literature. There have been only 2 instances, however, in which the cardiovascular dynamics have been investigated,[11,1] and to our knowledge there have been no reported angiocardiographic studies of this condition.

In this report the clinical and pathologic findings in 2 patients with cardiac glycogenosis are presented, emphasizing the hemodynamics and the angiocardiographic findings.

Clinical findings

The clinical findings in these 2 cases were similar and will be presented together. The angiocardiographic studies will be described separately.

Each patient was a full-term newborn male infant in whom symptoms first appeared at 4 months of age. Each had been examined at 6 weeks of age and found to be normal. One patient (Case 2) was re-examined by a pediatric cardiologist at 2 months of age, at which time no abnormalities were apparent. The parents had requested this examination because a sibling had died at 9 months of age from cardiac disease thought to be endocardial sclerosis.

At 4 months of age the parents of each child noticed poor gain in weight, circumoral cyanosis, and weakness. Because of these symptoms the infants were taken to their respective physicians, who made the diagnosis of endocardial fibroelastosis with cardiac failure in each case. Thoracic roentgenograms had shown generalized cardiomegaly with left atrial enlargement; electrocardiograms were interpreted as showing left ventricular hypertrophy with strain. Each patient was digitalized and responded moderately well for a short period

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to the usual regimen for cardiac failure. One patient (Case 1) was referred to the University of Minnesota Hospitals at 5 months of age because of continuing muscular weakness and cardiomegaly. The other patient (Case 2) suffered from repeated attacks of pneumonia and was referred to this hospital when 7 months of age for evaluation of intractable cardiac failure. In each instance the referring diagnosis was endocardial fibroelastosis.

The family history in Case 1 was normal. This patient had a healthy 2-year-old sister. In Case 2 the family history proved to be revealing. Besides 2 healthy brothers, ages 4 and 6 years, a brother had died when 9 months of age from cardiac disease thought to be endocardial sclerosis. The first symptoms in this sibling began at 4 months. A review of the necropsy records revealed, however, that the pathologic diagnosis was cardiac glycogen storage disease.

The physical findings in Cases 1 and 2 were similar. The infants appeared pale, wasted, and limp. Spontaneous movements of the body were very much limited. There was apparent lack of subcutaneous fat, whereas the skeletal muscles were firm and appeared normal in mass. Deep tendon reflexes were absent.

Respirations were rapid but not labored. The heart was markedly enlarged by percussion. The cardiac tones were of normal intensity, and a third sound was heard. The second sound was split, with

Fig. 1. Thoracic roentgenograms. *a and b,* Case 1. *a,* Frontal projection shows marked cardiomegaly. The strikingly convex prominence of the left upper cardiac silhouette (*arrow*) represents the huge left ventricle. The pulmonary vasculature is normal. *b,* Lateral projection. Prominence of the posterior and inferior portions of the cardiac density (*lower arrow*) also represents left ventricular enlargement. An additional prominence of the anterosuperior portion of the heart (*upper arrow*) represents enlargement of the right ventricular infundibulum and pulmonary trunk. The ventricular prominences produce a circular contour to the cardiac silhouette in this view. This is commonly seen in any type of congenital cardiac disease with biventricular hypertrophy. *c and d,* Case 2. The features are similar to the corresponding views in Case 1.

accentuation of the pulmonary component No thrill were palpable In Case 1 a soft systolic murmur was present along the left sternal border whereas no murmur wa heard in Case 2 The peripheral pulses were normal in each patient The liver and pleen were not palpable

Thoracic roentgenogram (Fig 1) revealed marked cardiomegaly The configuration of the heart in frontal and lateral views uggested biventricular enlargement Slight left atrial enlargement was demon trated on barium wallow The pulmonary vascular markings appeared to be normal The initial radiologic diagnosi in each wa endocardial sclerosi

Electrocardiograms and vectorcardiogram were available for re iew in each case (Fig 2 and 3) The P R interval was normal in Case 1 and abnormally short in Case 2 Extremely tall QRS complexes were present in all lead The QRS pattern sug ested marked left ventricular hypertrophy with strain and moderate right ventricular hypertrophy The vectorcardiograms were confirmatory howing combined ventricular hypertrophy predominantly left

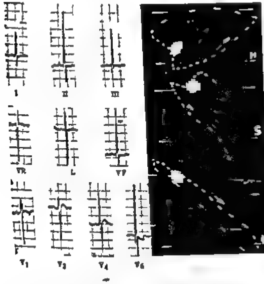

Fig 2 Case 1 Electrocard ogram (l ft) a d ector cardiogram (right) All 12 le trocardiograph leads were taken at one half tan lar l zat on The P R interval s normal n th a e 1h QRS xi in the frontal plane (tan lard lead) i n rmal QRS compl xe of extremely large oltage a present in every lead The QRS patt rn n the precordial lea l su est left entr ular hyper trophy with train and addit onal m derate r ght ventricular hypertrophy The QRS Ê l op i ea h f the three vectorcardiographic planes wa e tremely large and wa recorded at o e f rth sta d ardization The QRS Ê loop n the horizontal plane (H) suggests marked l ft ent ular hyper trophy with additional right e tr cul r h per trophy The QRS Ê l oops in the frontal plane (F) and sagittal plane (S) are norm l in in-cript on and orientation but are ma kedly al norm l n size

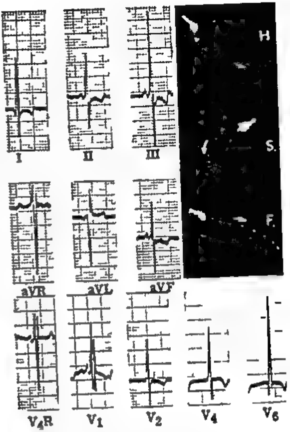

Fig 3 Case 2 Electrocardiogram and vectorcardiogram Lead I II aVR V and V were recorded at one half standardization and Lead V at one fifth standardization All other lead were recorded at normal tandardization The P R inter al i abnormally hort The mean QRS axi in the fr nt l plane (standard lead) slightly to the left There are extremel large QRS oltages in ver l ad The patterns in the precordial l a l uggest marked left entricular hypertrophy with train a d additionally mode ate right entri ular hypertrophy The QRS Ê loops were extremely large and were recorded at one fourth standardization The vectorcardiogram uggest bi entricular hypertrophy predominantly left H Hori ontal plane S Sagittal plane F F o tal plane

Laboratory data which were normal for both infants included blood counts and urinalyses fa t ing blood sugar glucose tolerance test epinephrine response test and glucagon response test In Case 1 an increase in glycogen in the peripheral lymphocytes was demonstrated by the period c acid Schiff sta n and confirmed by the absence of stainable material after treatment of the blood mears with dia tase Extreme gl cogenosis of skeletal muscle was demonstrated in each case with appropriate sta n ng of ti sue

Cardiac catheterization was performed in Case 1 and forward venou ang ocardiography wa done in each These studies will be described separate

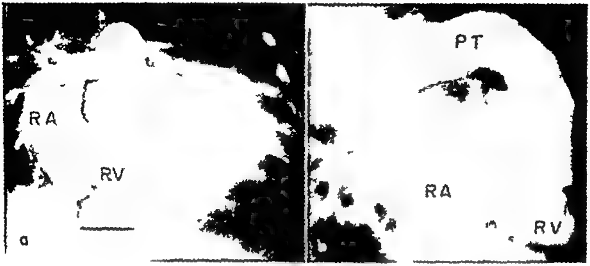

Fig. 4. Case 1. Cardiac glycogenosis and endocardial sclerosis. Forward angiocardiogram after injection into saphenous vein. Early films in the study demonstrate the right sided cardiac chambers. *a,* Frontal view. The enlarged right ventricle (*R.V.*) is compressed and displaced to the right by the huge left ventricle (unopacified left cardiac density). The pulmonary trunk is enlarged. *R.A.,* Right atrium. *b,* Lateral view, companion film to that in *a.* Pulmonary trunk (*P.T.*) is enlarged and forms the prominent convex density noted superiorly and anteriorly in the conventional lateral thoracic roentgenograms (Fig. 1). The right atrium (*R.A.*) overlies in part the density of the right ventricle (*R.V.*).

Cardiac catheterization (Case 1): Catheterization of the right and left sides of the heart was performed 13 days after admission. Oxygen saturations were determined by cuvette oximetry. Cardiac outputs were calculated by using an estimated basal oxygen consumption of 172 c.c. of oxygen per square meter of body surface per minute. Oxygen capacity was calculated from the hemoglobin concentration, assuming that each Gm. of hemoglobin combined with 1.34 volumes of oxygen. Local anesthesia was the only medication used. Catheterization of the left side of the heart was performed by introduction of a No. 5 Lehman catheter into the right brachial artery with retrograde passage to the left ventricle. Continuous pull-back pressures were recorded across the pulmonary and aortic valves during catheterization of the right and left sides, respectively.

A summary of the results of the catheterization is listed in Table I. There was no evidence either for obstruction to the exit of blood from either ventricle or for an intracardiac shunt. The low cardiac index (2.44 liters per square meter per minute) and elevated pulmonary arteriolar resistance were considered to reflect cardiac failure primarily of the left ventricle.

Angiocardiographic findings:

CASE 1. Forward angiocardiography was performed from a saphenous vein (Figs. 4 and 5). No evidence for intracardiac shunts or obstruction of outflow was present. The right atrium and right ventricle appeared to be enlarged. The left atrium appeared to be normal, whereas the left ventricle was massively enlarged, with an extremely thick wall. The left ventricular cavity remained dilated throughout the cardiac cycle.

The left ventricular outflow tract, aortic valve and ascending aorta appeared to be normal.

CASE 2. Forward angiocardiography was performed from a saphenous vein. The results of this test were interpreted as showing neither intracardiac shunt nor obstruction of either ventricular outflow tract. The right atrium and right ventricle appeared to be moderately enlarged (Fig. 6), whereas the left ventricle showed massive hypertrophy and dilatation (Fig. 7). There was slight left atrial enlargement. Serial films taken during ventricular systole and diastole demonstrated a near normal reduction in left ventricular volume during systole.

Hospital course: In each patient the hospital course was progressively downhill, associated with persistent cardiac failure and increasingly poor respiratory exchange. One patient (Case 1) died at 8 months of age (2 months after admission) and the other died 10 days after admission when 7 months of age.

Quantitative and qualitative analyses for myocardial glycogen were performed from tissue obtained at necropsy.[19] These studies revealed an abnormally high percentage (by weight) of normal glycogen. Studies for enzyme deficiencies were negative. These findings in each patient confirmed the diagnosis of Pompe's or Type II glycogen storage disease.

Pathologic findings:

SKELETAL MUSCLE BIOPSY: As part of the clinical study, skeletal muscle biopsies were performed. In each case large amounts of intracellular glycogen were demonstrated with the Best-carmine and with the periodic acid Schiff stains. Stainable glycogen disappeared when the tissue sections were exposed to diastase before staining. The skeletal muscle

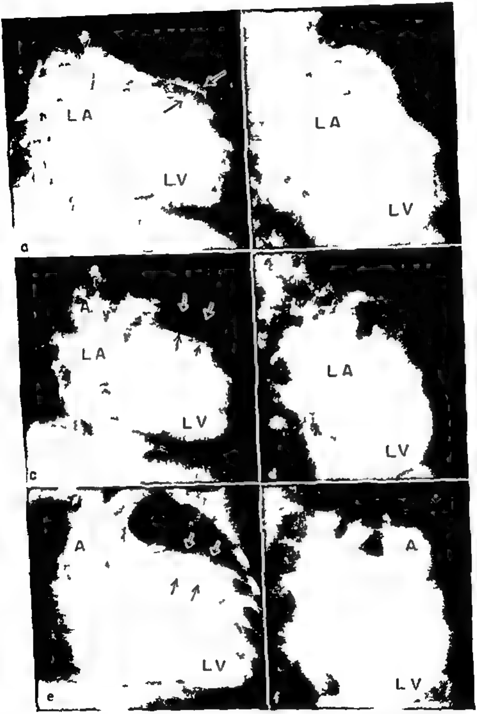

Fig. 5. Case 1. Continuation of angiocardiographic study shown in Fig. 4. Films demonstrate left sided cardiac chambers. *a*, *c*, and *e* are frontal views taken in sequence; *b*, *d*, and *f* are the respective companion films in lateral projection. In frontal projection, the left ventricle (*L.V.*) appears to have a huge cavity with a correspondingly thick wall (*facing arrows*). The prominence of the left ventricle in the frontal views corresponds to the prominence of the upper left cardiac border in the conventional thoracic roentgenogram (Fig. 1). In the lateral views the left ventricle occupies the posteroinferior aspect of the cardiac shadow. This corresponds to the posteroinferior prominence noted in the conventional lateral thoracic roentgenogram (Fig. 1). *Serial features: a and b*—Left atrial systole and ventricular diastole. Normal size of the left atrium (*L.A.*) and large dilated left ventricular cavity (*L.V.*). *c and d*—Next films in sequence show atrial diastole and ventricular systole. Enlargement of the left atrium with no apparent change in the size of the left ventricle. Aorta (*A*) is now visualized more clearly than in earlier films. *e and f*—Next films in sequence show normal left ventricular outflow to ascending (*A*) and descending aorta.

cell were extensively vacuolated The sarcous substance of the muscle fibers was compressed against the cellular membranes by the glycogen deposits (Fig 8)

HEART Each heart was greatly enlarged primarily as a result of the huge size of the left ventricle. The great vessels arose normally. The right atrium and right ventricle were moderately hyper

Fig 6 Case 2 Cardiac glycogenosis without endocardial sclerosis Forward angiocardiogram after injection into saphenous vein Early films in study demonstrate right sided cardiac chamber *a* and *b* are companion frontal and lateral views respectively *a* The right ventricle (*R V*) is enlarged and the medial wall is compressed by the large left ventricle (unopacified left cardiac density) The pulmonary trunk (*P T*) is large *R A* Right atrium *b* The right atrium (*R A*) and right ventricular chambers (*R V*) are in part superimposed As in Case 1 the anterosuperior prominence of the right ventricle and pulmonary trunk seen in the lateral conventional thoracic roentgenogram (Fig 1) correspond to the enlarged pulmonary trunk (*P T*)

Table 1 Case 2 Synopsis of cardiac catheterization

Sampling site	*Pressure (mm Hg)*	*Oxygen saturation (per cent)*
Superior vena cava	—	54
Right atrium	16/11 (Mean = 13) (a = 16 v = 14)	52
Inferior vena cava	—	54
Right ventricle	42/1?–17	—
Left pulmonary arterial wedge	25/16 (Mean = 20)	—
Left atrium	27/16 (Mean = 20)	92
Left pulmonary vein	—	92
Main pulmonary artery	40/3? (Mean = 34)	51
Right brachial artery	105/60 (Mean = 85)	94
Ascending aorta	105/6? (Mean = 90)	—
Left ventricle	105/10–20	—

Cardiac index = 2 44 L/M²/min (body surface area was 0 3 M²)
Total pulmonary resistance = 3 500 dynes sec/cm⁻⁵
Pulmonary arteriolar resistance = 1 310 dynes sec/cm⁻⁵

a = a wave v = v wave
Characteristic [illegible] the [illegible] elevated end-diastolic pressure in each [illegible] and the wide A-V oxygen difference

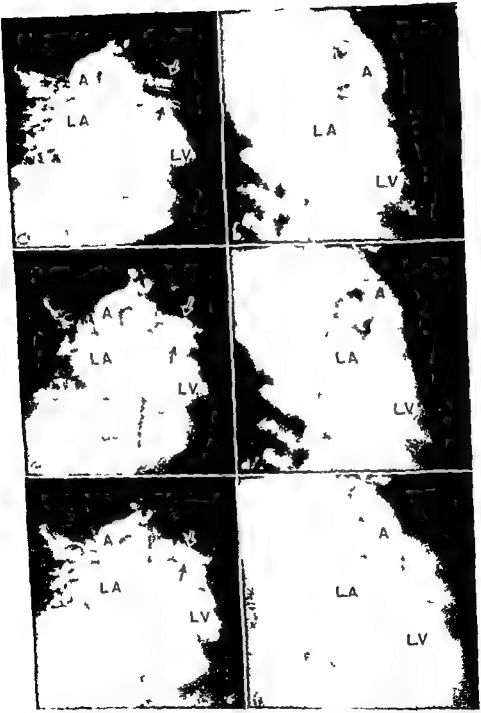

Fig 7 Case 2 Later phases of the study shown in Fig. 6 demonstrating left sided cardiac chambers *a c* and *e* are frontal views taken in sequence *b d* and *f* are the respective companion films in the lateral projection As in Case 1 the left ventricular prominence noted in the frontal and lateral thoracic roentgenograms (Fig 1) are confirmed by the angiocardiogram *Serial features a and b*—Large left atrium (*L A*) in diastole and partially contracted left ventricle (*L V*) in early systole The left ventricular wall is very thick (*facing arrows*) The ascending aorta (A) is opacified *c and d*—Later stage of ventricular systole The left atrium is enlarged and the left ventricle is fully contracted *e and f*—Ventricular diastole The left atrium is smaller and the left ventricular cavity has dilated considerably with thinning of the ventricular wall (*facing arrows*) The left ventricular outflow tract is normal These serial films demonstrate moderate contractility of the left ventricle in contrast to the dilated and fixed left ventricle in Case 1 wherein endocardial sclerosis was associated with cardiac glycogenosis

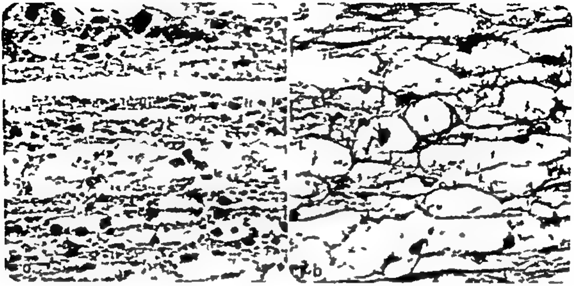

Fig 8 Case 1 Photomicrographs of keletal muscle biopsy *a* Most of the muscle fibers are vacuolated and appear cyst like Scattered throughout the field are dark staining deposits which represent glycogen (Best carmine tain ×500) *b* Skeletal muscle which was exposed to dia tase before staining Stainable glycogen has thereby been removed Cyst l ke area in the muscle f ber are more clearly seen (periodic acid Schiff stain ×500)

Fig 9 Gros pecimen of heart in Case 1 showing interior of right atrium (*R A*) and right ventricle (*R V*) The ventricle is dilated and hypertrophied The myocardium has a pale tran lucent appearance (photograph taken before fixation)

trophied and these chambers were moderately dilated (Fig 9) The left atrial chamber was normal in ize but its wall was moderately thickened In Case 1 having associated endocardial sclerosis the endocardial urface of the left atrium was lightly opaque (Fig 10 *a*) whereas the lining of the left ventricle was milky white and thickened The m tral valve and its chordal attachments in each case appeared to be functionally normal but there was l ht generalized thickening of the mitral leaflets in Case 1 In each case the chamber of the left ventricle was very large and the wall was ma ively thickened (Fig 10 *a* and *b* and 11) Generally the myocardium was pale and trans lucent. There was no evidence of obstruction of outflow of either the right or the left ventricle

Histologically low magnification views of the left ventricular myocardium howed a lacework or ponge l ke appearance (Figs 12 and 13 *a*) Endo cardial sclero is was present in Case 1 but in Case

Fig. *10.* Gross specimen of heart in Case 1. *a*, Interior of left atrium and ventricle demonstrating a normal mitral valve (*M V*), a very thick left ventricular wall (*L V*), and milky white thickening of the left ventricular and left atrial endocardium characteristic of endocardial sclerosis. *L A*, Left atrium. *b*, Left ventricular outflow tract and aorta (*A*). There is no evidence of subaortic or valvular stenosis (photograph taken before fixation).

2 the endocardium was within normal limits. With high magnification (Figs. 13,*b* and 14) a central clear cystlike space in each muscle fiber with no structural elements in it was the usual finding. The cytoplasm identified by cross-striations was concentrated peripherally next to the cellular membranes.

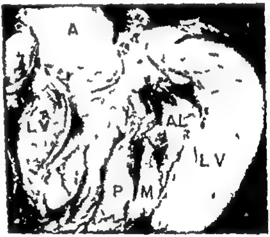

Fig. *11.* Case 2. Gross specimen of heart. Interior of the left ventricle and aorta (*after fixation with absolute alcohol*). There is marked hypertrophy of the ventricular wall (*L V*) and papillary muscles (*P M*, posteromedial; *A L*, anterolateral). The mitral valve and left ventricular endocardium appear to be normal. There is no evidence of subaortic or of valvular stenosis.

Comment

Patients with cardiac glycogen storage disease present specific clinical features which may distinguish this condition from a larger group of conditions (which occur in infants and children) referred to collectively as *primary endomyocardial diseases* by Lambert and Vlad.[8] In addition to glycogen storage disease of the heart, other conditions in this category are primary endocardial sclerosis (or fibroelastosis), anomalous origin of a coronary artery from the pulmonary trunk, myocarditis, calcification of the coronary arteries, and idiopathic myocardial hypertrophy. The features which characterize primary endomyocardial disease are: (1) cardiac failure in the first year of life, (2) massive cardiomegaly with relatively normal pulmonary vasculature, (3) absence of cyanosis of central origin, and (4) absence of significant cardiac murmurs.

Distinguishing cardiac glycogenosis from the other conditions in this group should be relatively simple since the skeletal musculature is also involved. Severe generalized muscular weakness is present. This is associated with an absence of deep tendon reflexes, a *normal* muscle mass, and apparent lack of subcutaneous fat. A positive skeletal muscle biopsy will establish the diagnosis of glycogen storage disease of skeletal muscle from which concomitant cardiac involvement may be

This condition is a nonsex-linked familial disorder. In a recent review[1] of the literature, 10 cases were found in which 2 or 3 siblings were affected; in another 7 cases the familial aspect seemed likely, although the diagnosis had not been substantiated in the siblings who manifested cardiac disease. The presence of cardiac glycogenosis in a sibling of Case 2 is another example of the familial tendency.

The electrocardiogram is frequently specific for this condition, as it was in our cases. The gigantic enlargement of the QRS complexes in *all* leads seems to be a feature peculiar to this condition. This phenomenon was better demonstrated in

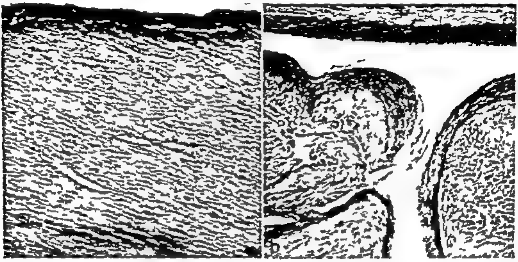

Fig. *12.* Case 1. Photomicrographs of the left ventricle demonstrates the lace-like appearance of the myocardium in cardiac glycogenosis. Endocardial sclerosis is also present. *a,* Thickened endocardium of the left ventricle forms dark zone above (elastic tissue stain, ×125). *b,* Junction of left ventricular sinusoid and ventricular cavity. Marked thickening of the endocardium and of the sinusoidal lining (elastic tissue stain, ×75.)

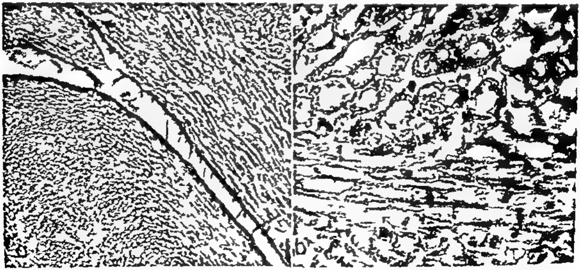

Fig. *13.* Case 2. Photomicrographs of left ventricle. *a,* Low-power magnification of left ventricular wall demonstrates lacework, vacuolated appearance of myocardium. The endocardium is minimally thickened. (Mallory's phosphotungstic acid hematoxylin stain, ×100.) *b,* High-power magnification demonstrates marked vacuolization of myocardial cells seen in longitudinal and cross sections. (Mallory's phosphotungstic acid hematoxylin stain, ×430.)

the vectorcardiogram which showed extremely large QRSsÊ loops with nearly normal contour and orientation in all three planes The short P R interval is another unusual feature which is probably specific for this condition Ehlers and associates[17] found a short P R interval in 17 of 21 cases in which electrocardiograms were available for review

The radiologic features of cardiac glycogenosis are very similar to those of primary endocardial sclerosis The massive cardiomegaly suggestive of biventricular hypertrophy the relatively normal or slightly plethoric pulmonary vasculature and left atrial enlargement are features seen in both conditions In our experience left atrial enlargement seems to be more prominent in cases of primary endocardial sclerosis than in cardiac glycogenosis

The most prominent angiocardiographic finding in the cases presented was a massively enlarged thick walled left ventricle In Case 2 in which there was no associated endocardial sclerosis the left ventricle appeared to be compliant during ventricular systole This was in contrast to the fixed dilated left ventricle demonstrated in Case 1 in which considerable endocardial sclerosis was present Therefore in cases of known cardiac glycogenosis a rigid left ventricle may be of assistance in the recognition of associated endocardial sclerosis

In neither of our cases was obstruction of either the right or left ventricular outflow tract suggested by the angiocardiographic study or at necropsy nor was there hemodynamic evidence of obstruction in the one instance (Case 1) in which cardiac catheterization was performed

This negative finding is in contrast to the observation of Ehlers and associates[17] who reported a previously unrecognized feature of diffuse cardiac glycogenosis namely muscular subaortic stenosis In their case the diagnosis was suspected clinically and proved hemodynamically by retrograde catheterization of the left ventricle These authors suggested that obstruction of the left ventricular outflow tract may have been present but unrecognized in previously reported cases of cardiac glycogenosis They proposed that an obstruction could be anticipated *from the* consistent presence of enormous left ventricular hypertrophy found at necropsy[17-1] This is an assumption which may have been valid for some cases but which to the best of our knowledge had never been tested by angiocardiography or catheterization until the present study

The findings in our cases indicate that

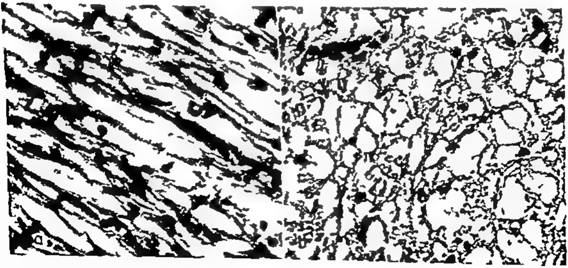

Fig 14 Case 1 Photomicrographs of left ventricular myocardium a Longitudinal section of myocardium demonstrates marked vacuolization of myocardial cells with the cytoplasm located at the periphery of each cell Cross striation are evident in the periphery of cells (Mallory s phosphotungstic acid hematoxylin stain ×500) *b* Cross sections of myocardial fibers show extensive vacuolization of the cell (Mallory s phosphotungstic acid hematoxylin stain ×500)

the presence of massive left ventricular hypertrophy need not be associated with subaortic stenosis. Furthermore, in cases of known cardiac glycogenosis the absence of a thrill and of an ejection type of systolic murmur at the base of the heart may be adequate clinical evidence for the absence of subaortic stenosis.

Summary

In 2 cases of glycogen storage disease of the heart, the clinical features which distinguished this condition from other forms of endomyocardial disease were: (1) lack of skeletal muscular tone and atrophy of subcutaneous fat, (2) electrocardiographic findings of huge QRS complexes and a short P-R interval, (3) the familial tendency (1 case), and (4) positive skeletal muscular biopsies for glycogen storage disease.

The angiocardiographic studies proved to be useful in evaluating the pathologic anatomy and hemodynamic status in each patient. In neither case were signs of subaortic stenosis observed by these studies. In the one case subjected to hemodynamic pressure studies, features of subaortic stenosis were not encountered.

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Age trend of mortality from coronary artery disease in women and observations on the reproductive patterns of those affected

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A striking feature of the epidemiology of coronary artery disease is the remarkable excess in mortality experience of men over that of women during early adult life and the decreasing sex differential thereafter (Table I). This phenomenon, combined with the demonstration of an increased risk of development of coronary artery disease in women who have had bilateral oophorectomy prior to natural menopause[1] has led to the conclusion that the menopause in women separates a period of relatively low and slowly rising risk of developing coronary artery disease from a period of rapidly rising risk. This interpretation may be restated as follows: among women the risk of developing coronary artery disease increases at a slower rate each year prior to menopause than afterward. One way to test this hypothesis is to plot the age specific death rates from coronary artery disease in females on a logarithmic scale. If the death rates increase at a constant rate with age, they will form a straight line. The slope of this line will indicate the rate of increasing risk with age. However, if the rate of increasing risk changes, the line representing the death rates will be deflected upward for an increase in rate of change and downward for a decrease.

In Fig. 1, age-specific death rates for females in New York State are plotted on a logarithmic scale for all causes of death, arteriosclerotic heart disease (including coronary disease), and cancer of the breast. For all causes the age specific death rates increase at a fairly constant rate from 30 years of age until 70, after which the rate of change increases. This is indicated by the upward deflection of the graph after age 70. The death rates for arteriosclerotic heart disease also rise constantly but more steeply than the total rates until age 70. The consequence of this is that arteriosclerotic heart disease makes up an increasing proportion of all deaths up to 70 years of age and a constant proportion thereafter. However, at *no point* in the age span does a sharp change occur in the rate of increasing risk of death from arteriosclerotic heart dis-

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Table I. Death rates from arteriosclerotic heart disease (including coronary disease) according to age and sex in New York State (exclusive of New York City), 1959-1960

Age (yr)	Males: Deaths per 100,000 population	Females: Deaths per 100,000 population	Male/Female ratio
25-34	12	2	6.0
35-44	84	15	5.6
45-54	369	71	5.2
55-64	976	332	2.9
65-74	2,198	1,151	1.9
75 and over	5,284	4,197	1.3

ease or in the rate of its increasing proportion of all deaths. In contrast, there is a definite decrease in the rate of increasing risk of death from cancer of the breast beginning at the approximate age of menopause.

Thus, it would appear that natural menopause does not mark a sudden change in the rate of increasing risk of coronary artery disease with age. For the hypothesis to have been supported, the slope of the line representing the death rates from arteriosclerotic heart disease after age 50 would have had to increase or the slope of the line representing death rates from all causes would have had to decrease. In the latter event, the constant slope of the line representing death rates from arteriosclerotic heart disease would have represented a departure from the general pattern of increasing risk of death with age and thus might have been interpreted as denoting a special effect of menopause.

In order to demonstrate a special effect of menopause, the data for cancer of the breast were presented. The marked decrease in the slope of the line representing death rates from this condition after age 40 indicates a change in the pattern of development of risk with age and is consistent with the hypothesis that estrogenic activity augments the risk of developing cancer of the breast and that its waning after menopause reduces the rate of increasing risk.[3]

Of course, due regard must be given to the possibility that the findings for arteriosclerotic heart disease are spurious because of errors of diagnosis and classification of causes of death. However, in order to have affected the conclusions with respect to the effect of menopause, there would have had to be a degree of misclassification before menopause different from that after.

Because of these observations, we have proceeded to test the hypothesis that women who develop coronary artery disease might be distinguished from nonsusceptible women during the premenopausal period by an indirect assessment of their endocrine status. Lilienfeld[4] has indicated a method for doing this by comparing cases and controls with respect to pregnancy experience and outcome. By means of this method, it has been shown that women with a recent myocardial infarction have approximately twice as much pregnancy loss from both stillbirths and abortions as do control subjects matched for age, race, and socioeconomic status.[5] The present study was undertaken to test these earlier findings.

Method of study

The pregnancy experience of a series of women with diagnosed arteriosclerotic heart disease was compared with that of a group having other diagnoses. Patients admitted consecutively to the medical service of a large county hospital (E. J. Meyer Memorial Hospital, Buffalo, New York) were interviewed and subsequently classified according to final clinical diagnoses into those with arteriosclerotic heart disease (International Classification of Causes of Death, 420.0, 420.1, 420.2) and those without. Each patient was interviewed as soon after admission as her condition permitted, and information was obtained in regard to age, race, religious preference, marital history, date of onset of major illness, menstrual history, pregnancies, live births, stillbirths, and spontaneous abortions. Diagnostic information was abstracted from hospital records after discharge and classification was made by one of the authors (A. C. R.). For the present analysis, 123 white women, 50 to 80 years of age, with a history of at least one

pregnancy were considered The lower age limit was to ensure that all women were postmenopausal at the time of the study whereas the upper limit was used because we thought that recall would be poor among those over the age of 80 Of these 123 women 59 had a diagnosis of arteriosclerotic heart disease either alone or in combination with other conditions and 64 had other diagnoses but not that of arteriosclerotic heart disease

In carrying out a retrospective study of hospital patients it is prudent to consider the possible effects of differences in hospital admission rates for each of the designated disease groups or classes of patients—in this case those with arteriosclerotic heart disease other diagnoses and history of pregnancy loss Berkson[8] has discussed the limitations of hospital data in this respect and has delineated the conditions under which valid comparisons may be made If unequal admission rates for women with arteriosclerotic heart disease and for those with other diagnoses are assumed the problem before us is whether hospital admission rates are equal for women with and without histories of pregnancy loss As far as we know there is no evidence that history of pregnancy loss per se has any relationship to subsequent hospital admission after menopause Therefore we may compare the rates of pregnancy loss for the two diagnostic groups without bias even though they are differentially represented in the hospital population

However there is evidence that pregnancy loss is associated with certain chronic conditions such as diabetes mellitus essential hypertension and thyroid disease of which at least the first two are considered to be important factors predisposing to arteriosclerotic heart disease Among the 59 women with a diagnosis of arteriosclerotic heart disease there were 20 (34 per cent) with diabetes 11 (19 per cent) with hypertension and 3 (5 per cent) with thyroid disease whereas among the 64 with other diagnoses there were 14 (22 per cent) with diabetes 14 (22 per cent) with hypertension and 4 (6 per cent) with thyroid disease (Table II) The possibility exists therefore that there is a selective factor (diabetes) which favors the admission of patients with high pregnancy loss to the arteriosclerotic heart disease group For this reason we will analyze pregnancy loss experience separately for diabetics

Another problem to be considered whenever the retrospective design is utilized is the prevalence incidence fallacy originally discussed by Neyman[2] The problem here is that the phenomenon under study in this case pregnancy loss may contribute to elimination of some subjects prior to the time of the study Thus if a history of pregnancy loss is associated with a higher risk of death in either of the diagnostic groups a survey of prevalence will reveal an excess history of pregnancy loss in the group less affected Since the most important known chronic disease correlate of pregnancy loss is diabetes a disease considered to be associated with increased risk of arteriosclerotic heart disease the attrition of pregnancy loss cases would most probably occur in this group thereby tending to lower the difference in prevalence of pregnancy loss between the patients with arteriosclerotic heart disease and those with other diagnoses

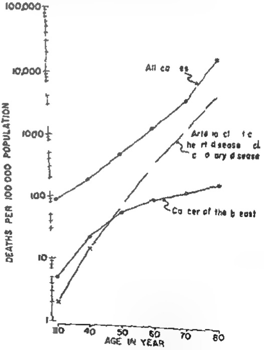

Fig 1 Death rates in females from all causes arteriosclerotic heart disease (including coronary disease) and cancer of the breast New York State (exclusive of New York City) 1950-1960

Table II. Frequency of selected diagnoses considered to be related to pregnancy loss according to diagnostic group

Selected diagnoses	A.S.H.D. (59)*		Other diagnoses (64)	
	Number of persons	*Per cent*	*Number of persons*	*Per cent*
Diabetes mellitus	20	34	14	22
Hypertension	11	19	14	22
Thyroid disease	3	5	4	6
Thyrotoxicosis	2	3	2	3
Myxedema	1	2	2	3

*Figures in parentheses indicate numbers of individuals.

The age distributions of the two diagnostic groups indicated that the group with arteriosclerotic heart disease was somewhat older than the residual diagnostic group (Table III). However, the two groups were comparable with respect to religious preference (Table IV), age at menarche, age at menopause, age at first marriage, and number of years married and menstruating (Table V). Nine patients (15 per cent) of the arteriosclerotic heart disease group and 12 (19 per cent) of the residual diagnostic group had histories of artificial menopause. The procedures utilized in these situations could not be reliably ascertained.

Results

There were 290 pregnancies among the 59 patients with arteriosclerotic heart disease and 242 pregnancies among the 64 women in the residual diagnostic group (Table VI). Two hundred eighteen (75 per cent) of the pregnancies in the group with arteriosclerotic heart disease resulted in live births and 72 (25 per cent) in loss; 17 (6 per cent) of the losses were due to stillbirths and 55 (19 per cent) to abortions. Among those with other diagnoses, 209 (86 per cent) of pregnancies resulted in live births and 33 (14 per cent) in loss, of which 7 (3 per cent) were due to stillbirths and 26 (11 per cent) to abortions. Thus, the patients with arteriosclerotic heart disease experienced about twice as much pregnancy loss as did the residual diagnostic group, and about the same number of livebirths. This was made possible by the fact that the patients with arteriosclerotic heart disease had 20 per cent more pregnancies than did the residual diagnostic group. In fact, the group with arteriosclerotic heart disease experienced on the average 4.9 pregnancies.

Table III. Study population according to age and diagnostic group

Age (yr.)	A.S.H.D.*		Other diagnoses	
	Number of persons	*Per cent*	*Number of persons*	*Per cent*
50-59	8	14	20	31
60-69	29	49	25	39
70-79	22	37	19	30
Total	59	100	64	100

*Arteriosclerotic heart disease (International List 420.0, 420.1, and 420.2).

Table IV. Religious preference according to diagnostic group

Religious preference	A.S.H.D.		Other diagnoses	
	Number of persons	*Per cent*	*Number of persons*	*Per cent*
Catholic	26	44	32	50
Protestant	33	56	30	47
Jewish	0	0	2	3
Total	59	100	64	100

Table V *Selected characteristics according to diagnostic group*

Characteristic	A S H D		Other diagnoses	
	Median	Interquartile range	Median	Interquartile range
Age at menarche	13	13–15	14	12–15
Age at menopause	48	44–49	47	43–49
Age at first marriage	21	19–26	21	18–24
Years of married menstrual life	22	14–28	22	16–26

Table VI *Pregnancy outcome according to diagnostic group*

Pregnancy outcome	A S H D (59)		Other diagnoses (64)	
	Number of pregnancies	Per cent	Number of pregnancies	Per cent
Live birth	218	75	209	86
Loss	72	25	33	14
Stillbirth	17	6	7	3
Abortion	55	19	26	11
Total	290	100	242	100

Figures in parentheses indicate numbers of individuals

Table VII *Pregnancy experience according to diagnostic group*

Number of pregnancies	A S H D		Other diagnoses	
	Number of persons	Per cent	Number of persons	Per cent
1–4	32	54	45	70
5 and more	27	46	19	30
Total	59	100	64	100

3.7 live births and 1.2 pregnancy losses whereas the residual diagnostic group averaged 3.8 pregnancies 3.3 live births and 0.5 pregnancy losses per person

Twenty seven (46 per cent) of the group with arteriosclerotic heart disease and 19 (30 per cent) of the residual diagnostic group had 5 or more pregnancies (Table VII) Thus the difference in total pregnancies between the groups is due to substantially more individuals in the arteriosclerotic heart disease group with relatively large (5 or more) numbers of pregnancies

There was a striking excess of women with arteriosclerotic heart disease who had 3 or more pregnancy losses (Table VIII) Thirteen (22 per cent) of the women in the group with arteriosclerotic heart

Table VIII *Pregnancy loss according to diagnostic group*

Number of losses	A S H D		Other diagnoses	
	Number of persons	Per cent	Number of persons	Per cent
0	30	51	40	62
1–2	16	27	23	36
3 and more	13	22	1	2
Total	59	100	64	100

that the relationship holds only for those with onset of arteriosclerotic heart disease prior to 60 years of age. The rate of pregnancy loss for those in whom arteriosclerotic heart disease manifests after the age of 60 is essentially the same as that for the residual diagnostic group. Thus it may be that the degree of estrogen deficiency necessary to produce frequent pregnancy loss is sufficient to substantially increase the risk of the early development of arteriosclerotic heart disease.

It would now be interesting to examine a group of women with frequent abortions and stillbirths and compare them with a suitable control group with respect to the development of manifest arteriosclerotic heart disease, as well as with respect to the prevalence of such well-established risk factors as high blood pressure, obesity, diabetes, and hypercholesteremia.

Summary

1. An analysis of the age-sex specific mortality rates from arteriosclerotic heart disease suggested that in women the rate of increasing risk remains constant throughout adult life and does not undergo sudden change at the time of menopause.

2. It was postulated that endocrine factors which affect the risk of developing coronary artery disease in women might be manifested prior to menopause and that these factors might also affect pregnancy experience and outcome. Fifty-nine white female patients between the ages of 30 and 80 years of age with diagnosed arteriosclerotic heart disease and 64 comparable patients with other diagnoses were compared with respect to pregnancy experience and outcome.

3. The patients with arteriosclerotic heart disease showed an excess of total pregnancies and pregnancy loss. The excess in pregnancies was interpreted as being the result of a compensatory mechanism. Patients with arteriosclerotic heart disease had a rate of pregnancy loss 1.8 times that for the residual diagnostic group. The difference in pregnancy loss between the group which arteriosclerotic heart disease and the residual diagnostic group was shown to be present only for women with onset of arteriosclerotic heart disease before the age of 60 years and for high order (3 or more) losses. Diabetes was not responsible for the observed difference.

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Serum free fatty acid and pressor responses to norepinephrine in healthy subjects and in those with ischemic heart disease

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Adrenergic release, together with its effects on circulation, induces lipolysis of fat depots and release into plasma of free fatty acids (FFA). Most of this fuel of muscular exercise[1] not consumed as energy is converted to triglyceride. Several FFA shorten clotting time in vitro[3] and their saturated third is strongly thrombotic in vivo.[4] Thus, release of FFA may be related to myocardial infarction, atherogenesis, and thrombotic disease. Indeed, comparisons of the contents of FFA in the sera of patients dying of various causes indicate much higher concentrations in those dying of ischemic heart disease (IHD) than of other causes,[5] although this may more plausibly reflect agonal adrenergic discharge than be a cause of the event.

The present study was undertaken to define the relative responsiveness of the release of FFA and of arterial pressure to norepinephrine in healthy men and in a comparable group of men with IHD, the latter established by myocardial infarction months or years before test.

During this period others[6,7] observed the excessive release of FFA into the serum of IHD subjects after smoking and showed that this was due to nicotine-induced adrenergic discharge of catecholamines. Such a response is attributable either to facilitated adrenergic release or to greater responsiveness of fat depots to the lipolytic action of catecholamines. The present data suggest that the former may be the case, since the latter is not.

Procedures

Studies were done in men in apparent good health and in another group of men of similar socioeconomic level and build who had recovered from myocardial infarction. The former consisted of 22 who were 37 to 56 years old (median 48) and whose ponderal indices (P.I.) ranged from 11.6 (heavy) to 13.1 (light) (median P.I. 12.4). The IHD group consisted of 14 who were 37 to 62 years old (median 49) and whose P.I. ranged from 11.9 to 13.0 (median 12.5). All came to the hospital from their homes after 12 to 14 hours of fasting from food and tobacco.

Tests were begun after 30 to 40 minutes of rest under conditions of quiet and reassurance by a procedure similar to that of Klein and associates.[9] Blood (B.) was sampled during the placement of a Cournand needle in an arm vein; a needle was placed in another vein for infusion, and a second sample of blood was drawn 15 to 20 minutes later (B 1). Norepinephrine (NE)

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Table I. Summary of fasting and post norepinephrine changes in serum FFA contents (μEq/L) in healthy and IHD subjects

	Healthy			Number of cases	IHD			Number of cases
	Mean	Maxima	Minima		Means	Maxima	Minima	
Sample								
B_0	373	570	200	21	583	1 070	280	11
B_{01}	443	800	240	21	675	1 000	300	11
Minute post infusion								
0	236	670	−10	21	190	420	10	11
10	310	680	−40	21	284	600	130	11
20	314	610	−30	21	226	540	50	11
30	219	970	−60	20	83	470	−70	11
45	36	740	−400	21	−10	240	−260	11
60	−50	120	−460	21	6	280	−420	11

*Since increments are made by [illegible] B_{01} the [illegible] excludes data on 1 healthy subject in whom this sample was lost and also [illegible] in 3 IHD subjects who developed angina and did not receive the full [illegible] μg of norepinephrine.

was then infused in saline (5 μg per minute for 15 minutes) and samples of blood were taken at 0, 10, 20, 30, 45, and 60 minutes after this infusion ended. Analyses of chilled sera for FFA were made promptly by the method of Schotz, Masson, and Page.[11] B and the final sample were also analyzed for cholesterol and triglyceride; since these showed no significant differences between groups nor changes after infusion of NE, the data are not listed.

Arterial pressure (auscultatory) and pulse rate were recorded frequently before, during, and after infusion. Two of the healthy and 5 of the IHD subjects were found to have mild hypertension* at rest. Onset of angina caused infusions to be terminated at 3, 5, and 8 minutes in 3 subjects with IHD. Data from these tests are not included in Table I. Those of hypertensive and anginal subjects are not included in means of pressure and pulse data.

Results

Data from analyses of serum FFA are summarized in Table I. Means of FFA in B were higher in subjects with IHD than in healthy men. Means of B 1 were slightly higher than those of B in both; these increments were not uniform, since increases of 50 μEq per liter occurred in 7 of 21 healthy and in 7 of 14 IHD subjects, with equivalent decreases in 1 of each group and small or negligible changes in other subjects. Distribution of fasting contents showed no association with body weight or with PI.

Post NE increases in FFA were measured from B 1. With wide individual variations, means of increments were similar in healthy and IHD subjects. Maximum increases were usually found in the samples taken at 10 or 20 minutes, although at 0 and 30 minutes in 1 each of 2 healthy men and at 0 minute in 2 IHD men. Respective increments at terminations of infusions of 15, 25, and 40 μg of NE during angina were 70, 270, and 30 mEq per liter at 0 or 10 minutes post NE, while in the last case a secondary rise of 1 180 μEq per liter occurred at 30 minutes, angina having recurred at about 20 minutes. As with fasting contents, responses to NE could not be associated with individual PI.

Preinfusion means of arterial pressure and pulse in the 20 normotensive healthy and 10 normotensive IHD subjects were respectively 113/75 mm Hg and 71 per minute and 106/73 mm Hg and 66 per minute. Means of maximum rises in pressure during infusion were respectively 12.5/10 and 19.4/10.4 mm Hg; the systolic increment was greater† in the IHD subjects. Pulse decrements were nearly equal, rates during infusion being 62 per minute

*Hypertension is defined as systolic 160 mm Hg or more and/or diastolic 95 mm Hg or more.

†Difference/standard error of differences of means 3.29.

Difference/standard error of differences of means 3.3.

in healthy subjects and 60 per minute in subjects with IHD respective means of minima of immediate postinfusion pressures were 106/72 and 99/65 mm Hg The 2 healthy hypertensive subjects and 3 IHD subjects who developed angina showed greater than average rises in pressure in the former 32/20 and 41/18 mm Hg and in the latter 28/14 36/12 and 70/16 mm Hg The first 2 of the anginal IHD group were hypertensive at rest whereas the patient with the most severe anginal pressor and FFA responses was not A response close to the mean was noted in one hypertensive IHD subject (resting pressure of 165/98 mm Hg) who did not experience angina

Comment

Responsiveness to NE induced release of FFA is similar and variable in healthy and IHD subjects of like ages and apparent general condition The somewhat higher fasting content of serum FFA in IHD subjects may reflect greater apprehension of or adrenergic release to the test situation The latter explanation would accord with greater responsiveness of such subjects to smoking [6] and also that those whose behavior pattern and serum lipid content are indicative of high IHD risk show larger excretions of norepinephrine[11] and 3 methoxy 4 hydroxymandelic acid[1] during working hours than do those of different temperament and constitution Although serum FFA is higher in obese than in normal subjects [13] no association of fasting FFA or response to NE with relative body weight was defined in these tests however the series is not large and none of the subjects was grossly obese

The greater systolic response of IHD than of healthy subjects to NE can plausibly be attributed to arteriosclerosis and diminished central arterial elasticity However the latter should also diminish bradycardic response[14] to NE and presumably the post NE decrement of pressure These differences were not found The angina associated with excessive pressor responses which was precipitated in 3 IHD subjects by doses of only 0 2 to 0 5 μg per kilogram of NE distributed over 3 to [illegible] minutes suggests a myocardial susceptibility to NE to which angina may have contributed

Conclusions

1 Mobilization of lipids as circulating FFA in response to norepinephrine (NE) was similar and individually variable in healthy and postmyocardial infarct (IHD) subjects

2 Systolic pressor responsiveness to small doses of norepinephrine was usually enhanced in IHD subjects as also in 4 of 5 subjects with mild hypertension of 3 post IHD 2 hypertensive and 1 normotensive rapidly developed angina and larger than average increments of pressure during intravenous infusion of norepinephrine at a rate of 5 μg per minute

I am deeply appreciative of the cooperation of those of the Cleveland Firemen s Union and of others healthy and with ischemic heart disease who volunteered for these tests

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Experimental and laboratory reports

Regulation of volume in postarteriolar vessels of the lower limb

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A good deal of work has been done in recent years to determine the *qualitative* direct and reflex responses of veins in the upper limb to various stimuli. The two principal techniques which have been used are (1) the relation of the change in volume in the upper limb to the change in venous pressure imposed by a restricting pneumatic cuff[2, 4] and (2) measurement of the change in pressure within a segment of superficial vein isolated by external occluding clamps, as an estimate of venous tone.[7-10]

The findings of these and other workers are summarized in Table I.

Very little work has been done to elucidate the qualitative or quantitative responses of the veins of the lower limb. These responses have considerable potential importance in a variety of situations including the normal variations in posture, the clinical management of low blood pressure states by postural adjustment, and in the action of many drugs. A study on the action of ganglion blocking agents in lowering systemic arterial pressure[14] does in fact suggest large increases in volume in the lower limbs of subjects given hexamethonium bromide in the upright posture.

We set out to attempt to assess not only qualitatively but quantitatively the capacity of the postarteriolar vessels of the calf and foot to react to some of these situations.

Methods

The principle of the method used was to determine the change in volume which occurs in the whole foot, or in a segment of calf, when the venous pressure is varied by passive postural change on a tilt table.

Changes in volume were recorded with double-walled air plethysmographs made of latex rubber (Fig. 1) on the principle described by Dohn[13] and Graf and Westersten.[16] The inner wall was 0.17 mm. thick and the outer was 0.51 mm. The maximum weights of the calf and foot plethysmographs used were respectively 40 and 90

Table I. Reported responses of venous tone in forearm or hand

Constrictor response	*Dilator response*
Loss of blood[4]	Heat (direct and indirect)[3]
Cold (direct and indirect)[4, 9, 21]	Fainting[2-4]
Pain or fear[3, 8, 24]	Cough[4]
Valsalva maneuver or hyperventilation[4, 9, 21]	Sympathetic block[3]
Inhalation 5 per cent CO_2[4]	Ganglion blocking drugs[4, 21]
Epinephrine[11, 22]	Nitrites[11]
Norepinephrine[11, 22]	Isopropylnorepinephrine
5-hydroxytryptamine[11, 22]	
Histamine[11]	

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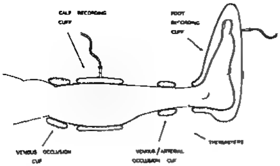

Fig 1 The arrangement of plethysmographs venous and arterial occlusion cuff and thermisters on the leg

grams The changes in volume in the encased portion of limb were calculated from the measured small changes in air pressure within the plethysmograph after calibration with air The changes in pressure were measured by a strain gauge/amplifier/pen recorder system

In most experiments the calf plethysmograph enclosed a 10 cm long segment of the calf at its greatest circumference (800 1 050 ml) and the foot plethysmograph enclosed the entire foot to the level of the malleoli (900 to 1 250 ml) The standard air pressure used was 3 to 5 mm Hg With the changes in volume observed the maximum increment of pressure was 1 5 mm Hg Previous findings[16] were confirmed that the expansion of an object surrounded by *the plethysmograph gave the same in*crement of pressure as the addition of an equal volume of air to the plethysmograph and that the relation between increments of volume and pressure was linear

The use of this type of plethysmograph in a temperature controlled room (19 to 21 C) permitted quantitative measurement of *blood flow* in the calf and foot by venous occlusion and at the same time measurement of much longer term *changes in volume* in any posture

It has been shown[16] that for measurement of blood flow this technique is essentially unaffected by changes in the temperature of the air or skin However for measurements of *change in volume* which takes place over 30 to 60 minutes a significant effect of temperature was found Variations in env*ironmental temperature* and drift of the recording system were insignificant but in some experiments which induced large increases in the flow of blood in the foot the temperature of the skin of the foot rose by up to 10°C

Experiments with a model showed that rises in temperature of this order could be corrected for when the mean of the rise in temperature of the inside and outside walls of the plethysmograph and the original volume of air within it were known In some in vivo experiments in which large increases in the flow of blood in the foot were produced over 2 to 3 minutes the lag in the rise in the temperature of the skin was sufficient to provide an independent check on this correction By this means the error in measurement of the increase in the volume of the foot accompanied by large changes in the temperature of the skin was judged to be less than 10 per cent No significant change in temperature occurred in the skin of the calf during these experiments

The subject lay usually in the prone position with the hip and knee slightly flexed and with the limb under investigation held immobile but relaxed in a splint The venous pressure was taken as the equivalent of a column of blood extending from the intersection of the mid axillary line with the horizontal plane through the upper border of the fourth chondromanubrial junction[17,18] to the center of the appropriate plethysmograph It is known *that at rest the superficial and deep venous* pressures in the lower leg are identical at the same horizontal level [9] In 2 normal subjects direct measurements of venous pressure were undertaken with a 0.5 mm O D catheter *in the internal saphenous* vein with the tip of the catheter in the middle of the calf segment usually covered by the recording cuff With foot down tilting a linear relation existed between the increments of measured and calculated venous pressure At zero calculated venous pressure measured venous pressures were 4.5 and 5.0 mm Hg respectively When the calculated venous pressure was negative with head-down tilting the actual venous pressure remained near zero

The standard technique was to tilt the subject in stages from 20 degrees head *down (−20) to 45 degrees (+45)* foot down and to measure the theoretical

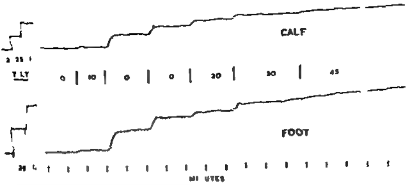

Fig 2 Simultaneous traces of change in volume of a 10 cm calf segment and of the corresponding foot during staged tilting from −20 to +45 degrees Calibration on left Note continued increase in volume at +45 degrees

change in venous pressure and the change in the volume of the limb segment at each stage The relation between the two was then plotted (cf Fig 3) the venous pressure was described as negative when it was calculated to be so This procedure was carried out before and after the stimuli to be described and the two venous pressure/volume curves were compared It was possible to alter the venous pressure in one limb alone by flexion at the hip in order to assess the influence of posture itself on the changes in volume On occasion the subject was suspended in the +45 degree position and short term responses of volume to stimuli were recorded

The temperatures of the skin and of the outer wall of the plethysmograph were measured by 0 5 cm diameter thermisters Pulse rate was obtained from continuous electrocardiographic recordings Brachial arterial pressure was measured either by brachial sphygmomanometry or by a brachial artery catheter and strain gauge with the elbow maintained at heart level When blood flow in the foot was recorded a 2 5 cm wide venous occlusion cuff was placed at the ankle and when blood flow in the calf was measured an arterial occlusion cuff was placed below the plethysmograph and a 5 cm wide venous occlusion cuff above (Fig 1) Measurements of blood flow were carried out with the subject [illegible] degrees head-down

The normal subjects used for this investigation were 11 men and 1 woman ages 21 to 34 years They were all physically normal and in particular none had evidence of varicose veins or arterial disease

Results

I Extent and site of changes in volume in lower leg and foot with passive change in posture

A VENOUS PRESSURE VOLUME RELATION When a subject was tilted foot-down in stages the changes in volume at each stage reached a plateau some 60 to 90 seconds after the change in position—the time depended on the flow of blood obtaining in the calf or foot Stabilization of the new volume was heralded by the appearance of clear cut respiratory waves in the trace demonstrating that the venous valves above were all open (Fig 2)

When the increments of volume in the

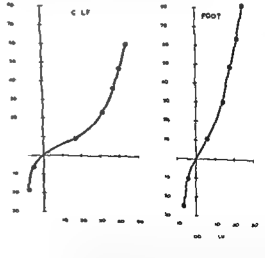

Fig 3 Relation between calculated venous pressure and volume change in 10-cm calf segment and in foot Zero Δ venous pressure = zero true venous pressure Zero Δ volume is taken as being at zero ... jects

Table II Relation between degree (°) of passive head down (−) or foot down (+) tilt, calculated venous pressure, and change in calf or foot volume (mean of 7 subjects)

Tilt (°)	Foot: Venous pressure (mm Hg)	Foot: Δ volume (ml)	Calf†: Venous pressure (mm Hg)	Calf†: Δ volume (ml)	Total§: Total Δ volume for lower leg and foot (ml)
−20	−25 2	−6 4	−18 4	−7 9	−21
−10	−10 4	−4 1	−6 4	−5 4	−14
−5‡	0*	0*	0‡	0*	0‡
0	+10 2	+6 1	+9 1	+16 8	+37
+10	+29 5	+13 8	+22 9	+31 2	+70
+20	+49 1	+18 0	+36 0	+36 9	+85
+30	+63 1	+21 2	+47 1	+40 4	+95
+45	+80 4	+24 6	+59 3	+43 [illegible]	+105

*Mean volume at 0° tilt: 1,159 ml. Mean flow of blood in foot: 1.63 ml/100 ml/min. Mean temperature of skin of foot: 31.4 C.
†Mean volume at 0° tilt: 963 ml.
‡Interpolated values.
§Calculated from data of Fig. (R... lt ... ls).

calf or foot were plotted against the change in venous pressure (venous pressure/volume relation), sigmoid curves were obtained, with minimal changes in volume at negative venous pressures, a maximal change through the range −5 to +25 mm Hg, and a progressive decrease in volume increments at higher venous pressures (Fig. 3) (Table II).

The over-all change in volume in the foot from −20 to +45 degrees under the ordinary conditions described was small, ranging from 23.5 to 40.5 ml in 7 subjects (Table II). The corresponding change in volume in the 10 cm calf segment was greater, ranging from 23.1 to 60.0 ml. There was a crude correlation of change in volume with the size of the foot or calf in different individuals.

B. DISTRIBUTION OF CHANGE IN VOLUME IN CALF. It was of some interest to discover the distensibility of different regions of the lower leg. The venous pressure/volume relation was plotted simultaneously in 5 different segments of a leg using 5-cm. wide, carefully fitted plethysmographs. It was apparent that the distensibility was disproportionately greatest in the most muscular segments (Fig. 4), and that the 10 cm. plethysmograph normally used recorded about 55 per cent of the change in total volume between ankle and knee. When the volume of the calf segment at each of the 5 different levels was calculated, with the estimated volume of bone (being nondistensible) subtracted, correlation with the change in volume between −10 and 55 mm Hg venous pressure suggested a close relation between distensibility and muscle mass (Fig. 5).

With these results used to calculate the change in volume taking place in the whole of one limb below the knee, the change in mean volume from −20 to +45 degrees under ordinary conditions in 7 subjects was 126 ml (Table II), or about 4.4 ml per 100 ml of leg.

C. NATURE OF LONGER TERM CHANGES IN VOLUME. When the dependent position was maintained for longer periods, there was a further slow increase in volume apparent in both the foot and the calf (Figs. 2 and 6). There was never a decrease in volume under these conditions; the increase in volume took place without a measurable change in the temperature of the skin or air, and the rate of increase was higher the greater the degree of dependency of the limb. Therefore, explanation as an artefact was dismissed. When a subject was tilted from −20 to +45 degrees and maintained in this position for 10 to 15 minutes, the extent of the slow increase in volume at +45 degrees was similar to the rise in base line volume on return to −20 degrees (Fig. 6). The rate of the slow rise in foot volume was

quite unaffected by stimuli which significantly affected the pressure/volume curve proper (see Results IID) and was of the same order as the increases in volume which we had measured on previous occasions by an overflow type of water filled foot volume measuring device

D VESSELS CONCERNED IN CHANGES IN VOLUME We tested in two ways the provisional assumption that the changes in volume in the limb segment up to 90 seconds after the change in posture took place almost entirely in postarteriolar vessels

1 Direct evidence on the changes in volume which resulted from arteriolar dilatation was obtained Graded exercise was used to produce increases in the flow of blood in the calf with the subject tilted at −20 degrees to empty the veins The post exercise blood flow and increase in volume were both measured Comparison of the increase in volume after exercise with that produced in the same subject by tilting to +45 degrees suggested that a more than twentyfold increase in the flow of blood in muscle would be required to produce the same change in volume as tilting (Fig 7) A similar procedure was carried out for the foot the changes in blood flow being induced by heating of the body or ganglion blocking agents and gave a similar estimate

2 During Experiment IB with the subject in the 45 degree foot down position the reduction in volume which occurred after 10 contraction relaxation cycles of the calf was measured in each of the 5 calf segments In a second experiment on the same subject under identical conditions a catheter (cf Methods) was used to measure the fall in internal saphenous venous pressure at a point in the middle of each of the segments after a similar period of exercise Upon the measured changes in ven

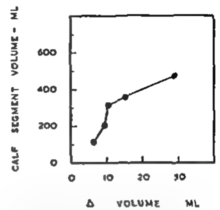

Fig 5 Relation between the *volume* of 5 segments of a calf (with estimated volume of bone subtracted) and the *change in volume* with change in venous pressure from −10 mm Hg to +55 mm Hg Same subject as in Fig 4

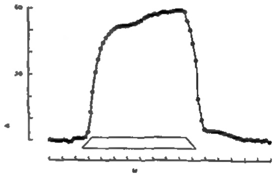

Fig 6 Longer term changes in calf volume with tilting from −20 to +45 and back to −20 degrees

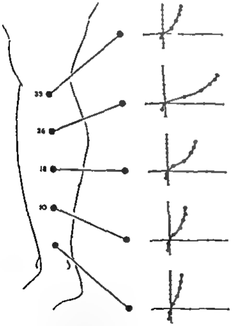

Fig 4 Venous pressure/volume relation for 5-cm calf segments at different levels Number represent distance in centimeters from internal malleolus Ordinates 10-mm Hg units Abscissae 10 ml units

Table III. Fall in volume in 5 segments of a calf after calf pumping measured and predicted from measured fall in venous pressure using data of Fig. 4

Cm above internal malleolus	Venous pressure fall (observed) (mm. Hg)	Volume reduction (predicted) (ml.)	Volume reduction (observed) (ml.)
33	26	2.6	5.2
26	40	12.5	12.2
18	43	6.3	7.8
10	45	4.0	3.9
4	47	2.5	2.4

pressure and the venous pressure/volume curves obtained in IB, we calculated the fall in volume in each segment on the provisional assumption that the change in volume which follows calf pumping is a function of the change in venous pressure. In 4 of the 5 segments there was good agreement between predicted and actual values (Table III).

E. LOCATION OF THE DISTENSIBLE VESSELS IN CALF. It was tacitly assumed that in the foot the changes in volume on tilting occurred in the postarteriolar vessels of the skin and subcutaneous tissue.

In the calf it seemed important to distinguish the proportion of the observed change in volume which was taking place in the vessels within the fascial envelope rather than in those of the skin and subcutaneous tissue. Therefore, the venous pressure/volume curve was plotted for a calf. The plethysmograph was removed, 1/2,000 epinephrine was iontophoresed[1] into the underlying skin, and 1/250,000 epinephrine was injected around the internal and external saphenous veins. The pressure/volume curve was repeated and found to be virtually identical to the first (Fig. 8).

F. EFFECT OF STANDING ON CHANGES IN CALF VOLUME. In 2 subjects an attempt was made to assess the effect of standing as opposed to passive dependency on calf volume. The increase in volume in the calf segment was measured when the posture was changed from 20 degrees head down to standing with the limb hanging free. This increment of volume was reduced by some 10 per cent when the weight of the body was evenly distributed between the two feet in short-term quiet standing.

II. Factors influencing venous pressure/volume relationship

A. WHOLE BODY COMPARED WITH ONE LIMB DEPENDENCY. There was no clear difference in the venous pressure/volume curves of the calf obtained in 6 subjects during whole body tilting as compared with dependency of one limb. When the results of repeated experiments in the same individual were grouped, there was a suggestion that the increase in volume was less with whole body tilting, but the difference did not lie outside the range of experimental error.

In the case of the foot, in 2 subjects (Fig. 9) it was clear that the increase in volume was less with whole body tilting by up to 7.5 ml. In the other 4 subjects, however, there was no detectable difference by this technique. The increase in volume was never greater with one limb dependency.

B. SYMPATHETIC BLOCK. Three different techniques were used to investigate the effects of sympathetic block on postarteriolar vessels: whole body heating, sciatic-femoral and saphenous nerve block, and intravenous ganglion blocking drugs.

In each case the venous pressure/volume

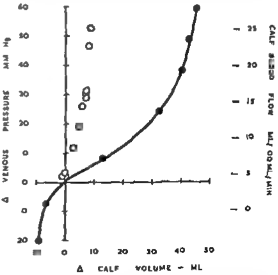

Fig. 7. Venous pressure/volume curve for a 10-cm. calf segment (*closed circles*) and, for comparison, the changes in volume in response to changes in blood flow in the segment (*open circles*) measured after graded exercise at −20 degrees tilt.

curve was determined for both calf and foot The subject then lay in the 10 degree head down position during the process of sympathetic block This permitted the measurement of blood flow in the calf and foot and of the changes in volume attributable to arteriolar dilatation there being a negative calculated venous pressure Maximum sympathetic block by the technique used was considered to have occurred when the temperature of the skin and the blood flow of the foot had reached steady maxima The venous pressure/volume curves were then redetermined

Heating of the body was carried out in 3 subjects by immersing the hands in a heated stirred water bath and covering the body with an electrically heated blanket (profuse sweating was produced)

Two per cent lidocaine was used to block the sciatic nerve at mid thigh and the saphenous nerve at the knee in 3 subjects This combination produced a very adequate sympathetic block to the foot as judged by the increase in the temperature of the skin and the flow of blood Although it seems almost certain that the sympathetic fibers to the calf vasculature are distributed via the sciatic nerve in another subject a femoral nerve and femoral periarterial block was effected

Intravenous hexamethonium bromide (25 to 40 mg) was given to 2 subjects and trimethaphan (20 mg) to one These doses were sufficient to lower the mean brachial arterial pressure by 15 to 30 mm Hg in the +45 degree position

The effects of these three techniques of sympathetic block are summarized in Table IV

In the foot there was always a significant increase in volume during the procedure at −10 degrees (5 5 to 20 0 ml) and skewing of the venous pressure/volume curve to give a further increase in volume at +45 degrees (9 0 to 29 0 ml) (Figs 10 and 11)

In the calf there was never a significant change in volume at −10 degrees (+1 0 to −3 0 ml) or at +45 degrees (−2 5 to +2 5 ml) (Figs 10 and 11) Femoral nerve and periarterial block produced as little change as did sciatic nerve block

Because we failed to detect a significant response of calf volume to the various forms of sympathetic block (in particular

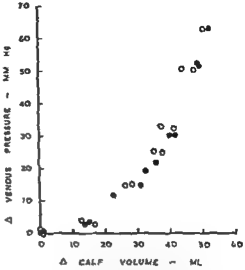

Fig 8 Venous pressure/volume relation for a 10-cm calf segment. Before (*closed circles*) and after (*open circles*) obliteration of skin vessels with epinephrine

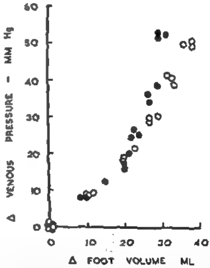

Fig 9 Foot venous pressure/volume relation in one subject *Closed circles* Whole body tilting *Open circles* One limb dependency Three tilts by each method

to hexamethonium) and because this finding was somewhat unexpected two additional semiquantitative techniques were tried

Two subjects were tilted from −10 to +45 degrees until after 7 to 10 minutes the slow phase of the increase in volume (Results Ic) was more or less linear Intermittent measurements of pulse and blood

pressure were made in order to detect any evidence of fainting. Thirty milligrams of hexamethonium bromide was then given rapidly intravenously. Within 3 or 4 minutes a fall in systolic blood pressure to less than 50 mm. Hg made it necessary to resume the head-down position. In each subject there was a pronounced increase in volume in the foot (4.6 to 12.4 ml.) and a just detectable increase in the calf (2.4 to 5.0 ml.) (Fig. 12).

Therefore, the experiment was repeated under identical conditions 2 days later except that the circulation in the skin of the calf segment was obliterated (cf. Results Ir).

The volume response of the foot was little changed, but the response of the calf to hexamethonium had become almost imperceptible (Fig. 12).

In one of these subjects, with the circulation of the skin of the calf obliterated, a simple comparison was made of the volume response to tilting before and 15 min

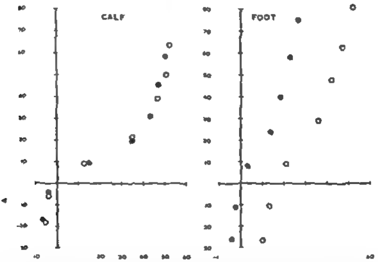

Fig. *10.* Venous pressure/volume relation for a 10 cm. calf segment and for the foot. Before (*closed circles*) and after (*open circles*) body heating. Foot blood flow before: 1.2 ml./100 ml./min. Foot blood flow after: 10.4 ml./100 ml./min.

Table IV. Effect of sympathetic block on the venous pressure-volume relation in foot and calf segment

Mean change	*Technique*		
	Body heating (3 subjects)	*Sciatic nerve block (3 subjects)*	*Ganglion blocking drug (3 subjects)*
Foot skin temperature (°C.)	+ 7.2	+ 5.4	+ 2.6
Blood flow (ml./100 ml./min.)			
Foot	+11.1	+ 8.9	+11.5
Calf	+ 0.2	+ 0.[illegible]	+ 0.5
Volume change at −10° (ml.)			
Foot	+14.0	+ 8.8	+14.[illegible]
Calf	+ 0.5	− 0.1	− 1.5
Volume change at +45° (ml.)			
Foot	+26.5	+1[illegible].0	+19.5
Calf	+ 1.2	+ 0.8	+ 9

utes after 30 mg. of hexamethonium intravenously. The foot volume was clearly greater at +45 degrees, whereas no difference apart from that due to a different rate of tilting was visible in the calf (Fig. 13).

In the subjects given hexamethonium bromide a study was also made of its effect on the slow increase in volume at +45 degrees after venous filling was apparently complete. No alteration in the rate of this increase was found in foot or calf.

A notable feature in each of the 3 subjects was the very marked tachycardia exhibited on foot-down tilting after administration of the ganglion blocking agent. In the 2 subjects in whom the +45 degree position was maintained for 10 to 15 minutes after completion of the plethysmogram, the tachycardia was ultimately replaced by an intense bradycardia, and a dramatic fall in arterial pressure to 80 and 50 mm. Hg systolic respectively. On rapid return to the −10 degree position a short-lived absolute increase in the flow of blood in the calf was observed in each case.

C. FAINTING. As part of another study a typical faint was induced by venepuncture in 3 susceptible subjects while they were tilted at +45 degrees. In each instance at

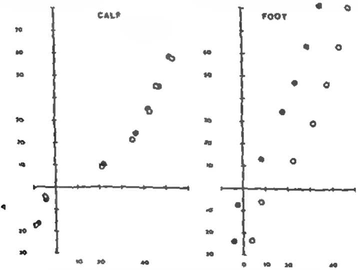

Fig. 11. Venous pressure/volume relation for a 10 cm. calf segment and for the foot. Before (*closed circles*) and after (*open circles*) 25 mg. of hexamethonium bromide intravenously. Foot blood flow before 3.2 ml./100 ml./min. Foot blood flow after 16.4 ml./100 ml./min.

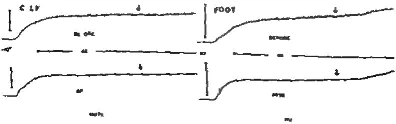

Fig. 12. Simultaneous changes in volume in foot and calf segment on tilting from −10 to +45 degrees. 30 mg. of hexamethonium bromide was given intravenously at the arrow. *Upper traces* before and *lower traces* after obliteration of the circulation of the skin of the calf with iontophoresed epinephrine. Calibration lines 50 ml. volume.

the commencement of the bradycardia a sharp rise in both foot and calf volumes was visible superimposed on the slow and constant rise due to the accumulation of fluid in the tissues The increase in volume before symptoms and low blood pressure made it necessary to return the subject to the horizontal was not however more than 5 ml for the calf and 3 ml for the foot and followed the fall in blood pressure On return to the head-down position there was a brief period of increased blood flow in the calf and foot

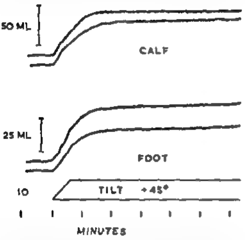

Fig 13 Simultaneous changes in volume in foot and calf segment on tilting from −10 to +45 degrees Lower trace of each pair is before and upper trace is 15 minutes after 30 mg of hexamethonium bromide intravenously The base lines of each pair are arbitrarily separated for clarity

D LOSS OF BLOOD Since all the previous stimuli had been dilator it was thought proper to test the effect of a constrictor stimulus Because it had previously been reported that a 600 ml venesection significantly increased tone in the veins of the forearm * this maneuver was performed on 2 subjects under conditions similar to those previously described in Section IIB In the first subject there was a small reduction in foot volume during bleeding and a steeper slope of the venous pressure volume curve in the foot with no change in the calf The second subject fainted during the venesection and the results were difficult to interpret

In a third subject 800 ml of blood was removed in an attempt to provoke a more striking effect As in the first subject there was only a minor reduction in foot volume during bleeding although there was a

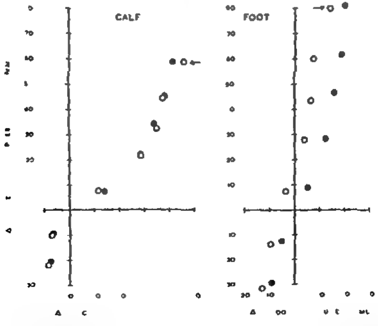

Fig 14 Venous pressure/volume relation for a 10-cm calf segment and for the foot. Before (*closed circles*) and after (*open circles*) an 800 ml venesection Foot blood flow before 2 0 ml /100 ml /min Foot blood flow after 1 5 ml /100 ml /min Arrows signify the points at which fainting occurred after venesection

more impressive change in the slope of the venous pressure foot volume curve. Between +30 and +45 degrees the subject suddenly fainted and as in the subjects of Section IIc there was a sudden increase in foot and calf volumes (Fig. 14).

It was clear that to obtain more clear cut results it would be necessary to induce a state of frank hemorrhagic shock.

Discussion

When a subject is passively tilted to a foot-down position, as with the technique used in this study, a pressure increment occurs in the larger veins and arteries of the leg roughly equivalent to the change in the height of the column of blood from the level of the heart to the point under consideration. This same rise in pressure probably takes place in arterioles, capillaries, and venules, although its actual value cannot be defined because of the modification of the hydrostatic effect by the variable arteriolar tone.

However, the *changes in volume* in the various vessels under these conditions depend not only on the pressure of blood within them but on the distensibility of their individual walls and of the surrounding supporting tissue, whether this be purely physical or a function of smooth muscle tone, and of other factors such as the accumulation of fluid in the tissues. It has been a basic assumption of venous occlusion plethysmography that the larger veins behave like collapsible tubes and up to certain limits can be distended with blood with minimal rise in pressure.[20] On the other hand, major arteries behave again within certain limits like elastic structures with very significant increments of pressure for given changes in volume.[23-25] The relation of pressure and volume in muscular arteries and arterioles is so dependent on the active tone of the vessel wall as to rather lack meaning in any simple physical sense.

In the face of an increased hydrostatic pressure, as occurs with passive tilting, these various vessels may all contribute to the increase in volume observed in the lower limb. So far as the whole body hemodynamic changes consequent on this sequestration of blood are concerned, the precise location of the blood is unimportant. On the other hand, when the factors which influence the pooling of blood in the leg are to be studied, such information is desirable and there is direct evidence (*q.v.*) to suggest that the major portion of the increase in volume of the leg which occurs with passive foot-down tilting is attributable to filling of postarteriolar vessels.

It has been shown (Results ID2, Table III) that the increase in volume in the calf on tilting is reversed by the rhythmic action of the muscle pump to a degree which is commensurate with the associated reduction in superficial venous pressure. Although this does not prove that the increase in volume takes place in veins, it does indicate that it is closely correlated with the venous pressure.

Evidence is balanced for[6, 7] and against[9, 10] a decrease in blood flow in the calf or foot on passive assumption of the erect posture. The importance of the arteriole in relation to the changes in volume with posture is, on this basis, uncertain. However, comparison has been made of the increase in volume in a calf segment after exercise or of that in the foot after whole body heating or sympathetic block with the changes in volume which occur at these sites on tilting (Results ID1). The results suggest that the proportion of the changes in volume observed in calf or foot which could be attributed to any reasonable variation in arteriolar tone is trivial. Similar evidence can be adduced from the work of Asmussen and associates[11] who studied the changes in volume in the distal 70 cm. of the lower limb after proximal arterial occlusion for 15 minutes with the subject horizontal or tilted 30 degrees foot down. With the subject foot-down, although the rate of filling of the limb was more rapid after arterial occlusion, the maximum volume of the limb did not exceed that achieved by passive tilting alone.

A related problem which we have considered is where in the foot or the calf the distensible vessels lie. *In the hand* 85 per cent of the tissue consists of skin and nondistensible bone or tendon[17] and it is likely that the distribution is similar in the foot. Moreover, the main pathway for the venous drainage of the foot is by way of the plexus of subcutaneous veins on its dorsum. It seems probable, therefore, that in t

foot the distensible vessels lie principally in the skin and subcutaneous tissue

With regard to the calf we have direct evidence (Results IE) that the increase in volume in the calf on tilting occurs deep to the deep fascia for obliteration of the vessels of the skin and of the long and short saphenous veins produces an insignificant alteration in this increase (Fig 8) The close correlation that we observed between muscle mass and the increase in volume in different segments of the calf with tilting (Results IB) taken together with the anatomic evidence emphasizing the great size of the venous sinuses in the soleus muscle [33] strongly suggest that it is the *intramuscular veins* which chiefly account for the observed changes in volume

The results summarized in Table II suggest that when normal subjects passively assume the upright posture more than 250 ml of blood pools in the two legs below the level of the knees If allowance is made for the different techniques used and for the variable proportions of the lower limbs studied this value is of an order similar to that obtained by other workers [14 31 34 36]

These other workers have not however correlated venous pressure with changes in volume and did not note the sigmoid nature of the venous pressure/volume relation that we observed for both calf and foot (Fig 3) At positive hydrostatic pressures the shape of the curve is as would be expected from the concept of veins as collapsible tubes The remarkable feature is perhaps the fact that the vessels of the calf bounded ultimately by the rather dense deep fascia of this region are capable of such great distention The sharp reduction in the $\Delta V/\Delta P$ relation at negative calculated hydrostatic pressures is in a sense artefactual but implies that vein size has become a function of tissue blood flow only

It seems certain that the slow increase in volume observed in both the calf and the foot after the appearance of respiratory waves in the traces has signified that the venous valves are open is due to the accumulation of fluid in the tissues (Results IC) A similar conclusion has been reached by other workers [34 37 38]

With a change from passive dependency to quiet standing we observed a reduction in the increase in calf volume by about 10 per cent presumably due to the increase in muscle tone With more prolonged standing there appears to be sufficient muscular movement to reduce the venous pressure at the ankle by 7 to 40 mm Hg [39] There is presumably a corresponding reduction in the venous volume of the lower leg More active use of the calf muscle pump produces a very considerable lowering of venous pressure in superficial[19] and deep [9] veins of the lower leg and a substantial reversal of the pooling of blood in foot and calf (Results ID2 Table III)

Using the venous pressure/volume relation as the test system we found that the postarteriolar vessels of the foot behave qualitatively in a fashion similar to that of the vessels of the hand and forearm with respect to body heating sympathetic nerve block ganglion blocking drugs loss of blood and less certainly change in posture (Results IIA B D Table IV) On the other hand the quantity of blood removed from or added to the foot in the 45 degree foot down position by these maneuvers was small never being more than 29 ml Moreover of this volume no more than half could be attributed to a change in venous tone the other half was presumably due to a change in arteriolar tone Thus so far as the foot is concerned changes in venomotor tone would appear to play a very minor part in the whole body response to these stimuli

The results of our attempt (Results IIA) to detect changes in postarteriolar tone in the foot and calf in response to foot down tilting are inconclusive unless the convincing evidence of venoconstriction in the foot in only occasional subjects represents a true physiologic variation between individuals

We could find no significant change in the venous pressure/volume relation for the calf with any of these stimuli However by using semiquantitative techniques (Results IIB) we were able to achieve a much greater fall in blood pressure with hexamethonium and presumably therefore a more rapid and profound ganglion block Under these conditions there was a small increase in volume in the calf This response virtually disappeared when we attempted to obliterate all skin vessels and subcutaneous veins in the calf segment

There was also evidence of a minor increase in volume in the calf with fainting (Results IIc) but this was no greater than might be expected from the associated arteriolar dilatation

The deduction is that either the deep veins of the calf are unresponsive to those maneuvers which affect the tone of the postarteriolar vessels of the foot hand and forearm or such a response as occurs is undetectable by the rather sensitive technique we have employed The former explanation is consistent with the findings of Donegan[10] that in animals stimulation of peripheral nerves or the sympathetic chain produced no change in the caliber of deep veins whereas the superficial veins were strikingly constricted Naked eye comparison of the internal saphenous vein with the sinuses in the soleus muscle emphasizes the delicacy of the walls of the latter although they do in fact contain some smooth muscle (personal observations) We can find no account of the innervation of the intramuscular veins of the calf

Our observations with regard to the calf are at variance with those of O Donnell[14] who found large increments in volume in the lower leg in the 60 degree foot down position in response to intravenous hexamethonium bromide in dosage that was rather smaller than that which we used employing mercury in rubber strain gauges as the measuring device His results may be explained in part by a greater *rate* of venous filling due to the increase in the flow of blood in the skin after the drug The fact that the increased rate of increase in volume in the lower leg which he observed continued throughout the 8 to 14 minute period of observation also suggests an increased rate of formation of fluid in the tissues although we ourselves were unable to detect such a response (Results IIB) Another possible explanation is that there was arteriolar dilatation in the muscle associated with bradycardia and a fall in arterial pressure such as we observed in our subjects who were given rather larger doses of hexamethonium bromide The mechanism of this latter syndrome following an intense tachycardia may be a fainting reflex from the empty heart[41] Possibly also his subjects superficial calf veins had an unusual capacity to dilate

We would summarize our findings by suggesting that although the postarteriolar vessels of the foot behave like smooth muscle tubes with a sympathetic innervation those within the deep fascia of the calf are better considered to be intrinsically passive tubes with their adjustment of volume determined solely by the tone and activity of the skeletal muscle which surrounds them In terms of the volume of blood sequestered in the leg below the knee when the upright posture is assumed the latter vessels are much the more significant

Summary

1 A technique for measuring the changes in volume which result from alteration in postarteriolar tone in the lower limb is described using air plethysmography and a tilt table

2 The relation between change in venous pressure and change in volume with passive change of posture has been studied for the foot and for a segment of calf and has been used to measure changes in postarteriolar tone

3 With passive change of posture the short term changes in volume in the foot appear to occur chiefly within superficial vessels whereas the changes in volume in the calf occur within deep intramuscular veins

4 The responses of the postarteriolar vessels of the foot to postural change sympathetic block and loss of blood are qualitatively similar to those reported in the upper limb

5 The measured changes in volume in the foot in response to these stimuli are small the maximum observed was 29 ml of which no more than half could have occurred in veins

6 There was no evidence of changes in volume occurring within the deep fascia of the calf as a consequence of change in intrinsic venous tone

7 Although superficial veins behave like innervated smooth muscle tubes it is suggested that the deep veins of the calf behave like passive tubes surrounded by skeletal muscle

We are most grateful to the normal subjects who volunteered for these often uncomfortable procedures for the invaluable technical assistance of Mrs Joa Lyd SRN and to Professor C

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A quantitative evaluation of functional stenosis of the semilunar valve

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A qualitative solution of functional stenosis of a semilunar valve was published by Dr. D. R. Chisholm[1] in 1937. More recently, Dr. V. A. McKusick devoted adequate space to this argument in his 1958 text on cardiovascular sound. Both authors describe the action of the semilunar valve during systole as one of trigonoidation. Blood moving through a semilunar valve during the ventricular ejection phase empties the semilunar pockets and presses the free margins of these pockets toward the artery (pulmonary or aorta) wall. The free margins of the pockets are nonelastic or of constant circumference and under normal pressure-flow relationships are not quite long enough to open against the circular arterial wall.[1] This feature obviously makes for quick filling of semilunar pockets at the outset of diastole.

It is the purpose of this report to demonstrate quantitatively all degrees of functional stenosis, normal and abnormal, during ejection which result as a consequence of any given increase in systolic separation of the commissures one from the other of a semilunar valve, the separations being due to arterial dilatation at the valve level.

The configuration of the semilunar valve opening during systole is normally not quite circular but that of an equilateral trigonoid[1] or a quasi-triangle in which the sides are circular arcs of equal curvature and length. It is clear that if the free margins of the semilunar pockets could open to a circular form, the systolic area A (Fig. 1) of the valve opening, being circular, should have a maximum value. Let the radius of this circle be a_1 (Fig. 1). If we define the distance from the center of the valve opening to any one of the three commissures as α, the radius of the trigonoid, it is clear that α is slightly greater than a_1 during systole, and the valve opening is normally slightly less than A maximal (= 7.07 sq. cm., arbitrary). When an increased pressure-flow relationship moves the commissures further apart during ventricular ejection (dilatation of the artery wall), α, the radii of the trigonoid, increases and the area A (Fig. 1) decreases. The complete relationship is shown in Fig. 1, where A, the area of the valve opening during ejection, is any ordinate under the curve and is given for increasing values of α from the limit A maximal where $\alpha = a_1$ to the limit A minimal where $\alpha = 1.21\ a_1$.

Shown above the dotted region of Fig. 1 are the percentage decreases in the area

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A at the given increases in α the radii of the trigonoid The minimal value of A is seen to be 4 27 sq cm or a functional stenosis of 39 6 per cent This limit is certainly *never reached clinically* for at this end point the free edges of the semilunar pockets are (without stretching or increasing their original lengths) just long enough to reach from one commissure to the other on a *straight* line that is the trigonoid becomes an equilateral triangle with sides of zero curvature and blood moving through the valve opening is required to produce the unlikely curvature of zero on the free edge of each semilunar pocket during ejection Hemodynamically the increased *pressure flow relationship* at the valve opening which increases α (the radii of the trigonoid) also tends to *increase* the curvature on the free edges of the semilunar pockets Consequently a zero curvature or triangular opening* can very probably never be reached However systolic dilations of $\alpha = 1\ 19\ a_1$ (Fig 1) must be fairly common clinically At this point trigonoidation would presumably cause an effective functional stenosis of about 18 2 per cent The normal systolic murmur which can regularly be measured from a *sound pickup located in the artery* just above the valve opening[3] is presumably now loud enough to cause a Grade 2 3 6 ejection murmur which is easily audible with a stethoscope at the pulmonic or aortic valve areas Murmurs of this intensity are not ordinarily accompanied by a palpable thrill At grades of functional semilunar stenosis beyond about 18 2 per cent and approaching but not reaching 39 6 per cent dilatation during systole apparently carries α beyond the value $1\ 19\ a_1$ but not reaching $1\ 21\ a_1$ (Fig 1) Here the functional stenosis almost certainly has a *pathologic hemodynamic implication* (*see below*) and the associated basal ejection murmur is of intensities greater than 3 6 Such intensities are often associated with a palpable thrill at the pulmonic valve area and less frequently at the aortic valve area Ejection clicks aortic or pulmonary are also common with systolic dilations of the semilunar valve rings

Basal systolic functional murmurs of intensities 1 3 6 are common as a normal

*See Appendix

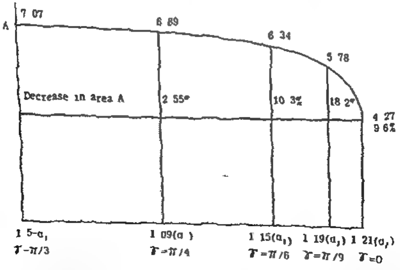

Fig 1 Any ordinate A under the curve defines the area of a normal semilunar valve during the ejection phase of systole On the abscissa are shown the increasing length of α the radii of the trigonoid (*see text*) The magnitude of the values for A are shown as ordinates under the curve and the percentage *decrease in the area* A are given at specific increases of α over the dotted region The values of the angle γ made by the tangent t (Fig 2) and the corresponding side of the included equilateral triangle QQ Q are given which determine the particular value of α by (2) of the Appendix

finding in infants and children Similar ejection murmurs of intensities 1 2/6 are equally common in young healthy adults Since blood flow is increased with exercise these normal ejection murmurs may be made more intense by increasing trigonoidation Moreover since the pulmonary valve is more easily dilatable the functional ejection murmur is a more common finding at this valve area

Abnormal conditions associated with high cardiac output (anemia hyperthyroidism A V fistula beriberi etc) commonly lead to sufficient functional stenosis *of semilunar valves (trigonoidation) to be* the cause of ejection murmurs of Grades 1 5 6 intensities When these factors are corrected much of the functional stenosis of the semilunar valves vanishes and the associated murmur often disappears completely Many other factors which increase the pressure flow relationship through normal semilunar valves exist in the area of congenital heart disease but cannot be given space in this report

Discussion

The qualitative development of functional stenosis (trigonoidation) of the semilunar valves has been established experimentally [1] The quantitative basis for functional stenosis of the semilunar valves as depicted in Fig 1 is geometric or mathematical and is discussed briefly in the Appendix It appears certain that the ejection area A (Fig 1) operates along a curve of the form shown It appears almost certain that operation occurs along this curve between but not reaching the maximal and minimal limits shown at the left hand and right hand ends respectively of the curve in Fig 1

The exact point on this curve which is associated with an ejection murmur of given intensity is based at this time on an educated guess and suggests a need for further experimentation

Appendix

The two right triangles θ r and γ t are similar Here t is the tangent to the arc Q Q′ at Q′ and always remains at 90° with respect to r

The dotted area in Fig 2 is the area A of the trigonoid and may easily be shown to be

$$(1) \qquad A = \frac{\pi a_1}{3\gamma}\left\{1 - \frac{\sin 2\gamma}{2\gamma}\right\} + \frac{\pi^2 a_1^2 \sqrt{3}}{9}\left\{\frac{\sin\gamma}{\gamma}\right\}^2$$

and

$$(2) \qquad \alpha = \frac{2\pi a_1}{3\sqrt{3}}\left\{\frac{\sin\gamma}{\gamma}\right\}$$

In Equation (1) the first member on the right defines the total part of the area *A exterior to the equilateral triangle QQ Q* (Fig 2) In the limit as $\gamma \to 0$ this area vanishes and the minimal value of A (Fig 1) is reached The second member on the right in Equation (1) defines the area

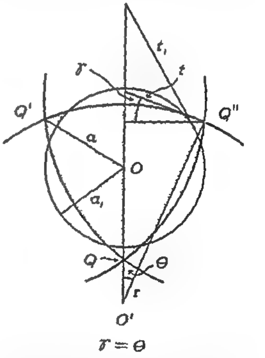

Fig 2 Geometry of a semilunar valve opening during the ejection phase of systole The commissures are at Q Q and Q The circle of radius a_1 indicates the *maximal* value of the area A of the valve opening which might obtain if the opening were circular The circumference of this circle is the sum of the free edges of the three semilunar pockets Arterial dilatation permits the dotted area to obtain It is the area A of an equilateral trigonoid or quasi triangle of 3 sides each composed of circular arcs of equal curvature The radius of the trigonoid is α The right triangles r θ and t γ are similar (*see text*)

of the equilateral triangle QQ'Q' In the limit as $\gamma \rightarrow o$ this quantity reduces to

$$(3) \qquad \frac{\pi a_1^2 \sqrt{3}}{9} = \frac{3a^2 \sqrt{3}}{4}$$

The right hand side of Equation (3) is obviously the area of an equilateral tri angle if the distance from its center to one apex is α

In the limit for A maximal we have $\gamma = \pi/3$ and $\sin\gamma = \sin 2\gamma = \sqrt{3}/2$ Formula (1) now gives

$$1 = \pi a_1^2 \left\{ 1 - \frac{3\sqrt{3}}{4\pi} \right\} + \frac{3a_1^2 \sqrt{3}}{4} = \pi a_1^2$$

the area of a circle of radius a_1 (Fig 2)

Finally the curvature of the circular arc forming the side of the trigonoid at any time during ejection is $3\gamma\ \pi a_1$ which is $1/a_1$ when A is maximal and zero when A is minimal These are the limits *between which* the ejection phase of the semilunar valve must operate If under marked and prolonged increases in the pressure flow relationship the length $2\pi a_1$ 3 of the free edge of the semilunar pocket should stretch the associated permanent increase in A is still defined by Equation (1) and is pro portional to πa_1 for all ejection phases of trigonoidation

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Correlation between subjective and objective measures of correspondence between different systems of vectorcardiography

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For several years the vectorcardiographic loops obtained by different lead systems have been compared by a subjective method.[1] The ideal correspondence was denoted by a rating of 10, whereas 0 denoted that the two loops showed no correspondence at all.

This method, although satisfactory in practice, has all the drawbacks of its subjective nature. This was the reason that we introduced objective measures for the differences between vectorcardiographic systems.[2,3] These measures give the relative displacement of the points of the loop when the loop is transformed from one lead system to another. The calculation of the displacement can be made in an "isotropic" way (measure D) if the prevailing directions of the heart vector are not taken into account, or in an "anisotropic" way (measure δ) if allowance is made for the frequency of occurrence of different directions of the heart vector.

In our last paper[3] the main problem was to study the relations of lead systems averaged over a fairly large number of subjects. It was pointed out, however, that the agreement of the systems can also be evaluated for each individual separately. It is the purpose of this paper to investigate the correlation of different criteria for correspondence, using such individual data.

Material and method

The calculations to be described here were applied to the vector loops of 24 cardiac patients.

The three lead systems compared were those originated by Frank,[4] McFee and Parungao,[5] and Burger and associates. They will be referred to by the letters F, M, and B, respectively.

Subjective comparison. This was done in two ways. First, ratings for the correspondence between frontal and horizontal projections were given by the three authors separately and then averaged. Although the omission of the sagittal projection emphasizes the influence of the right-left vector component, later experience gives us the impression that the final result cannot be much in error because of this shortcoming.

A second and principally better com

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parison was obtained by constructing three dimensional vector loops from metal wire. A simple device, not to be described here, allowed this to be done with sufficient accuracy and in a relatively short time. Then the correspondence of these wire figures was estimated and indicated by a rating without consideration of the orthogonal projections. This method is essentially better than the first one, not only because all three orthogonal components of the heart vector are now equally weighed, but because the vectorcardiogram is essentially a three-dimensional curve. Although it *can* be described by orthogonal projections or by orthogonal components, it has a meaning in itself apart from orthogonality or from any mathematical system used in displaying it. It is this consideration that induced us to replace the former comparison of projections, however easy it might be, by the comparison of spatial loops.

To increase the statistical evidence, the three ratings of the comparisons F-M, M-B, and B-F for each subject were averaged, accepting the loss of detail so introduced. Thus for each subject the mutual correspondence of the three lead systems was indicated by two subjective criteria. The first (P) gives the correspondence of the two orthogonal projections, the second (S) gives the correspondence of the spatial loops.

Objective comparison. As mentioned above, the transformation of a vectorcardiographic loop from one system to another can be used to calculate the displacement of the end point of the heart vector in two different ways, yielding two different measures for the displacement, viz., D (isotropic) and δ (anisotropic).

In addition, there is a "true" distance of isophasic points of loops in two different lead systems. This distance was measured for 5 isophasic points on each pair of loops being compared. To obtain a relative measure (T) for the average true distance, the square root of the average squares of the five distances was divided by the average size of the loops.

$$T = \frac{\sqrt{\Sigma a^2/5}}{\sqrt{\bar{X}^2 + \bar{Y}^2 + \bar{Z}^2}}$$

Just as in the case of the subjective measures, the objective measures for the correspondence of the three combinations F-M, M-B, and B-F were averaged.

For each pairwise combination of the five quantities P, S, D, δ, and T a scattergram could be drawn containing 3×24 points. From this figure the correlation could be judged very roughly. All these figures will not be reproduced because a much better measure of their connection is given by the correlation coefficient r. We shall restrict ourselves to these coefficients without giving the regression equations. Since a correlation ($r \neq 0$) may be caused by chance, the (95 per cent) confidence limits must also be indicated.

Because of the limited number of cases, the calculated r's are not equidistant from their upper and lower confidence limits, so that the results may be represented in the form

$$r = 0.46\ (0.26 - 0.62)$$

Since S and P are measures for the agreement, but T, D, and δ for the difference of two vectorcardiograms, negative r's occur, meaning that an increase in the one quantity is accompanied by a decrease in the other.

Results and discussion

The first combination to be mentioned is δ-T (anisotropic-true). As could be expected, the values of these two objective measures of the difference of systems are almost equal. Their correlation coefficient $r = 1.00$. Therefore we shall omit δ in the following considerations. Then four quantities remain, viz., the two subjective measures P and S and the two objective ones T and D, giving six combinations.

In Fig. 1 the six correlation coefficients are shown. They can all be considered to be significant, although some of them are rather small. As could be expected, the isotropic measure D is less well correlated with the subjective measures S and P than is T, the true distance. Therefore, in further investigations we can rid ourselves of D in favor of T (or δ).

Comparing the correlations of S and P with the true difference T, we see that S is slightly better correlated with T than is P. This difference is not statistically significant. Still the fact that the mutual cor-

relation between S and P deviates significantly from r = 1 00 indicates that there must be a real difference The introduction of the sagittal projection in the subjective comparison giving P would possibly further reduce this difference

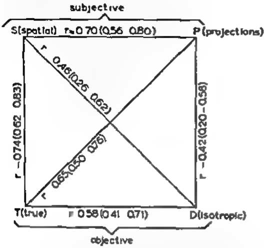

Fig 1 Correlation coefficients between subjective and objective criteria for the correspondence and the difference respectively of the individual VCG loops in three lead systems The numbers in parentheses give the range corresponding to the standard error in the coefficient

All in all it does not appear to be worth while to construct wire loops in all cases for so little gain in correlation

It might seem disappointing that the best correlation S T between the spatial wire loops and the true difference does not score better than r = 0 74 But we must not forget that the aims of the subjective and of the objective methods are different In the first one criteria that are of diagnostic significance receive higher weight attention is given to right or left preponderance clockwise or counterclockwise inscription in the projections etc The objective methods however lead us to a result along a purely mathematical route and therefore blindfolded This is the price we have to pay for objectiveness

Elaborating the relation S T somewhat further we have plotted the corresponding values of S and T in a scattergram (Fig 2) It gives the regression i e the average

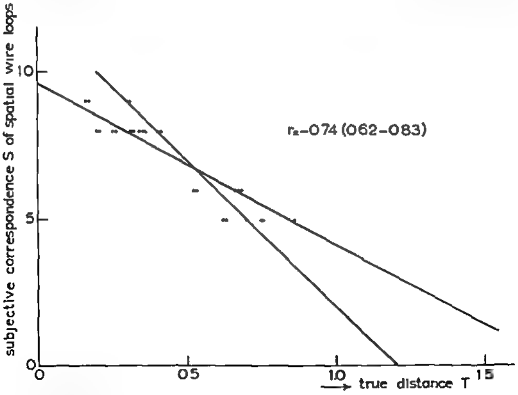

Fig 2 Scattergram of the relation between the relative average true distance of isophasic points and the rating for the correspondence of spatial wire loops The regression lines have a slope that can be considered to be satisfactory

dependence of the one quantity on the other. That two lines are drawn is a consequence of the imperfect correlation ($r \neq -1$). But taking a slope in between the slopes of the two lines, we see that a rating of 10 in the individual evaluation corresponds to a relative average true distance (T) of isophasic points of 0 as it should. A rating of 0 corresponds to a T of 1.3. Said otherwise, one unit in the range of individual ratings for the correspondence of spatial loops stands for a relative average true distance in position of corresponding points of 0.13 (13 per cent). This situation can be considered to be satisfactory.

Summary

The agreement between vectorcardiograms obtained by different lead systems may be judged by various subjective and objective methods.

To test the validity of these methods, the results were studied when they were applied to vectorcardiograms obtained by the lead systems of Frank, McFee and Burger. For each individual case the three vectorcardiograms were compared pair-wise from the loop-projections (P) as well as from spatial wire models (S), and the degree of *similarity* was evaluated subjectively and expressed by a rating between 0 and 10.

Objectively, the *difference* between the vectorcardiograms was given by the relative average true distance (T) between isophasic points on the loops, as well as by the extent of the displacement brought about by a linear transformation designed to transform the one system into the other (δ). Correlations between P, S, T, and δ were calculated and were all found to be significant. T appeared to be interchangeable with δ ($r = 1.00$). Of the other correlations, the best one was between S and T (or δ) ($r = 0.74$), although the difference with P and T was only small. The regression coefficient proved to be plausible. For purposes of comparison of systems the use of wire models has only slight advantage over loop-projections.

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Hemodynamic consequences of experimental ventricular pre-excitation

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Ventricular pre-excitation syndrome (Wolff-Parkinson-White syndrome) has been claimed to be an electrocardiographic abnormality which has no adverse effect on the patient except that attacks of tachycardia occur in some cases.[1,2] Hemodynamic studies in this condition are few. They are mostly based on indirect measurements, and the results are inconclusive.[4,5]

Ventricular pre-excitation can be produced easily in the experimental animal, and its electrocardiographic appearance resembles closely the characteristic features described in human beings.[9,11] Both in patients and in animals the basic abnormality is the asynchronous contraction of the ventricular muscle. We assumed, therefore, that the production of experimental ventricular pre-excitation in dogs might enable us to investigate parameters which would elucidate the pathophysiologic consequences of the asynchronous ventricular contraction. The purpose of this study is to describe the results of such experiments.

Materials and methods

The experiments were performed on 30 mongrel dogs which ranged in weight between 6 and 16 kilograms. Anesthesia was induced by 30 mg. per kilogram of Na thiopentone and was maintained with intravenous pentobarbital as needed. The chest was entered through a longitudinal sternal split, and the pericardium was opened widely. The right atrium and the anterior surface of both ventricles were thus exposed. Ventilation was maintained by a mechanical respirator. One of the standard leads of the electrocardiogram was continuously recorded. A bipolar electrode was placed on the right atrium, and the atrial activity was transmitted to a pulse generator which, in turn, stimulated the lateral subepicardial surface of the right ventricle or the anterior surface of the left ventricle.[11] The delay through the generator was shorter than that in the normal conduction system. This resulted in a premature excitation of a circumscribed area of a ventricle and led to an asynchronous contraction of the myocardium. Pressures were measured in the right and left ventricles by catheters introduced via the saphenous vein and the carotid artery. They were obtained through Statham strain gauge transducers and recorded on a Sanborn Poly-Viso recorder. In 10 dogs, relative beat-to-beat changes in aortic blood flow were measured and recorded continuously with the aid of a noncalibrated rotameter. In 10 dogs a strain gauge arch was sutured to the an-

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terior surface of the right ventricle parallel and close to the septum Since its feet were not stretched and only minimal tension was applied while suturing it ventricular segment length was thus recorded These hemodynamic parameters were recorded during normal conduction during normal beats alternating with pre excitation beats and during continuous ventricular pre-excitation

Results

Because of the dissimilarities seen in the hemodynamic alterations in alternating normal and pre excitation beats and during continuous ventricular pre-excitation the results of these two types of observations will be presented separately

1 *Alternating pre excitation beats* It was observed that the first pre excitation beat following a series of normally conducted beats resulted in a lowered systolic pressure in the ventricle and a somewhat elevated diastolic pressure in the same beat The aortic flow was reduced and there was also a diminished shortening of the segment length The following intrinsic beat which was normally conducted brought about a rise in the ventricular systolic pressure to a level higher than control and the diastolic pressure dropped to normal Similarly the stroke volume and the shortening of the segment length of this normally conducted beat were greater than both the pre excitation and the control beats A series of alternating beats showed these changes to be constant (Figs 1 4)

2 *Continuous ventricular pre excitation beats* After a series of normally conducted beats the first pre-excitation beat produced the same kind of changes in hemodynamics as described above Continuation of the pre excitation led to gradual return toward normal of the values measured As can be seen in Fig 5 the second pre-excitation beat produced a systolic pressure higher than that produced by the first beat and also higher than that produced by the third beat These variations in the height of the systolic pressure continued for a number of beats (varying in different dogs) until the systolic pressure stabilized at a level somewhat lower than the control pressure Similarly the elevation of the diastolic pressure after the first pre-excitation beat was also diminishing after a few successive beats and became stabilized at a level only slightly higher than the control diastolic pressure (Figs 5 and 6) The record of the aortic flow demonstrated a marked immediate reduction in the flow at the initiation of the pre excitation with a quick return to nearly control levels (Fig 7) Corresponding changes were seen in the segment length of the myocardium (Fig 8) It is worth noting that even if equilibrium is established during a series of pre excitation beats a single normally conducted beat brings about a change following which a number of pre-excitation beats are again necessary to restore equilibrium

Discussion

Since most patients with pre excitation syndrome suffer no recognizable clinical manifestation of their disease few attempts have been made to measure directly the consequences of premature contraction of a part of the ventricular musculature on cardiac hemodynamics[4,5] A number of investigators made electrokymographic studies in a search for premature contraction of the part of the ventricle pre-excited by the delta wave The results of these studies were inconstant[6,7] which could be due to the inaccuracy of the methods used and to the differences in the mechanical response of the ventricles in different patients Alterations in the contour of the jugular phlebogram measurements of the electrical mechanical time intervals such as the interval between the P or Q wave and the beginning of the rise in pressure in a peripheral artery interpretation of the quality of the first and second heart sounds and their components—all have served as parameters for investigating the hemodynamic response to the Wolff Parkinson White syndrome (WPW)[4,5,8] There is only a limited number of reports of studies in which the above mentioned methods were used and each study incorporated only a small number of patients Therefore it is not surprising that the conclusions are so varied These indirect methods do not seem to be sensitive enough to reflect adequately the mechanical results of discoordinate action of a part of the ventricular wall Ferrer[5] and her group described

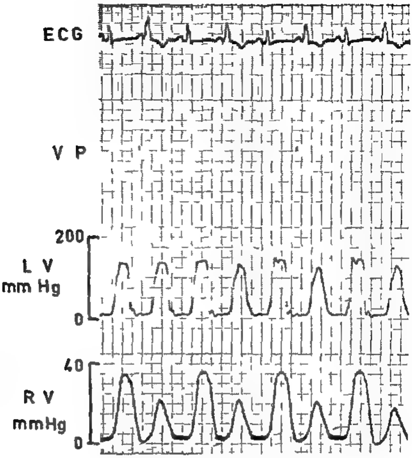

Fig. 1. Alternating pre-excitation beats. Note marked changes in the systolic and slight changes in the diastolic pressure in the right ventricle (R.V.), much less pronounced in the left ventricle (L.V.). Pre-excitation applied to the right ventricle. Paper speed 50 mm./sec. V.P. = Ventricular pre-excitation.

hemodynamic changes in 2 patients during catheterization of the right side of the heart. They observed a delayed contraction of both ventricles on the basis of the relationship of electrical to mechanical heart action. Experimentally produced WPW-like beats in dogs enabled Prinzmetal[10] and his group, using a high-speed moving picture camera, to observe a localized area of premature contraction of the ventricle. Yet there are no detailed hemodynamic studies known to us in the experimental animals. We believed, however, that in the presence of discoordinate ventricular action some type of mechanical alteration in cardiac dynamics, even though of only a minor degree, should occur. Since we had previously made some observations on the electrocardiographic features of experimentally produced ventricular pre-excitation,[11] we have adapted this method and have made direct observations on intracardiac pressures, aortic blood flow, and myocardial segment length in dogs with normal beats and with experimentally produced WPW-like beats. This type of experiment enables one to study the effects of a single discoordinate beat as well as of long series of such beats.

In our study, if one looks at the record of a dog with a long succession of pre-excitation beats, the impression one gets is that left and right ventricular pressures, aortic blood flow, and myocardial segment length are well within control range. However, if one carefully compares these parameters during pre-excitation and normal beats, one sees that there is a slight but definite difference. This is manifested by a slightly lowered systolic pressure and

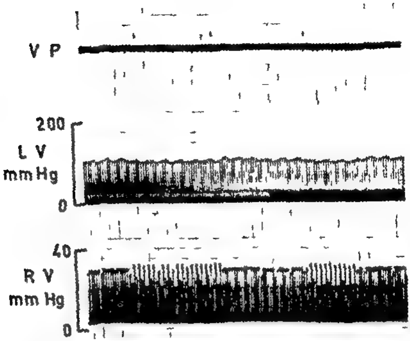

Fig 2 Same as in Fig 1 with slow paper speed (7.5 mm/sec) Note higher systolic pressure in the intermittent normal beats than in the control beats

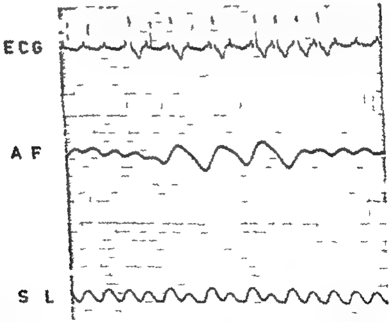

Fig 3 Alternating beats and a short run of pre-excitation beats Note marked changes in *A F* and *S L* during alterations and return toward normal during continuous pre-excitation The intermittent normal beats have higher A F and shorter S L during systole than do the control beats Pre-excitation applied to left ventricle Paper speed 75 mm/sec *A F* Aortic flow (upward deflection indicates increased flow) Time lag is due partially to flowmeter tubing *S L* Segment length (upward deflection indicates shortening)

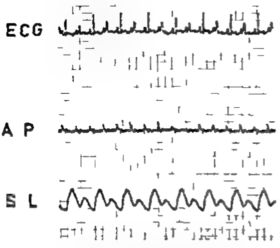

Fig. 4. Alternating pre-excitation beats. Note reduced shortening of the segment length (*S.L.*) during systole and elongation during diastole in the pre-excitation beats. The intermittent normal beats show marked shortening of S.L. in systole and less elongation in diastole than do the control beats. Pre-excitation applied to the right ventricle. Paper speed 75 mm./sec. *A.P.*, Atrial potential.

aortic blood flow even though the systolic shortening of the segment length of the ventricle does not seem to be altered. Since a part of the ventricular muscle is not working in concert with the rest of the ventricle, being refractory because of pre-excitation, a smaller mass of ventricular fibers appears to take over the function of expelling an almost normal amount of blood at a pressure close to control levels. This would indicate, therefore, that the myocardial muscle fibers, apart from the pre-excited and now refractory ones, are made to work with a greater force of contraction. This is shown by the recordings of an unchanged myocardial segment length in spite of a smaller efficiently contracting mass.

From these observations it appears that during long runs of pre-excitation, slight hemodynamic changes are produced and the values differ little from the control ones because of a compensatory mechanism affecting ventricular contractility. However, if one generates pre-excitation beats alternating with normally conducted beats, a myocardial compensatory mechanism might not be able to set in with the rapid beat-to-beat changes. This assumption is proved by the observation described and shown in the alternating pre-excitation beats. The first discoordinate beat produces a fall in systolic pressure, a fall in aortic flow, and less pronounced shortening of the segment length. These lead to an augmented residual volume, an elevated diastolic pressure in the ventricle, and elongated end-diastolic segment length. The next beat results from an excitation spreading only through the normal conduction tissue. It expels more blood at a pressure even higher than that of the control beats because of synchronization of contraction and increased force of contraction due to the elevated end-diastolic pressure and fiber length. The following discoordinate beat will again result in a reduction in pressure, flow, etc. This series of events can be repeated as long as alternating beats are repeated. The conclusion can thus be drawn that alternating pre-excitation in the experimental animal (and most likely also in man) produces marked alteration in cardiac hemodynamics from beat to beat and cannot be called simply an electrocardiographic abnormality.

In the transition from normally conducted to a long run of pre-excitation beats one finds a number of beats in which hemodynamic alterations occur. The first WPW-like beat in a series is similar to a single pre-excitation beat. The next few WPW-like beats gradually expel the residual volume of blood by an increased force of contraction due to elongated muscle fibers combined with an unchanged cardiac inflow. This sequence of events is shown by a rising systolic pressure and increasing aortic flow and by a diminishing end-diastolic pressure. This compensatory mechanism is of heterometric type dependent on Starling's law. However, since in a few beats there is a stabilization of pressure and flow at a value only slightly lower than the control value, it appears that increased force of contraction of the ventricle is being maintained without a concomitant elongation of the myocardial fibers. This compensatory mechanism has been described as the homeometric type.[12, 13] The increased force of contraction is shown in the recording by the equal heights of the deflection of the segment length during the control and the latter pre-excitation beats in spite of the fact that fewer muscle fibers

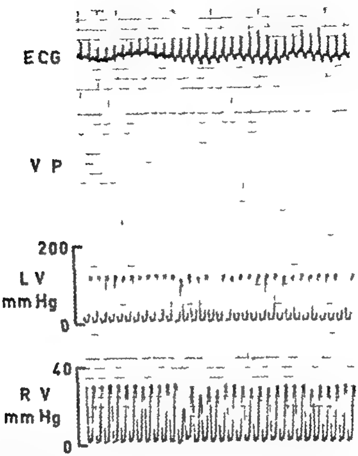

Fig. 5 Continuous ventricular pre-excitation. Note marked drop in systolic pressure and rise in diastolic pressure in the right ventricle (*R V*) and less pronounced in the left ventricle (*L V*) in the first pre-excitation beat. During the following pre-excitation beats a gradual return toward normal values are shown. Pre-excitation applied to the right ventricle. Paper speed 10 mm/sec. *V P*, Ventricular pre-excitation.

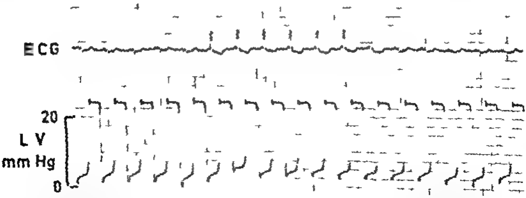

Fig. 6 Continuous pre-excitation beat. Note transient rise in diastolic pressure in the ventricle when pre-excitation started and gradual decrease toward control values later on. Pre-excitation applied to the left ventricle (*L V*). Paper speed 50 mm/sec.

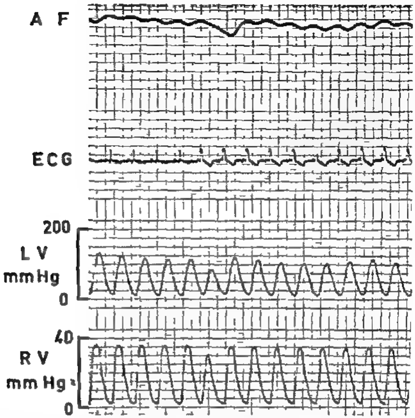

Fig 7 Continuous pre-excitation beats Note sudden drop in aortic flow (A F) and systolic pressures in both ventricles with the first pre-excitation beat Return toward control values sets in during the next pre-excitation beats Pre-excitation applied to the left ventricle (L V) Paper speed 25 mm/sec R V Right ventricle

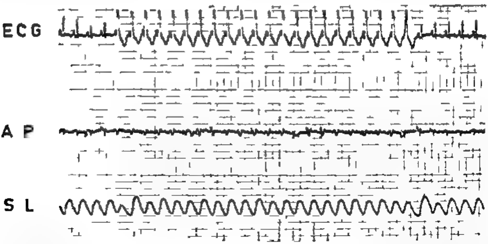

Fig 8 Continuous pre-excitation beats Note reduced systolic shortening of the segment length (S L) in the first pre-excitation beat and shorter than normal S L in the following one The S L returns to the control level in the next few beats and remains so during ventricular pre-excitation At restoration of normal conduction the first beat shows again a shorter S L than the control one Pre-excitation applied to the right ventricle Paper speed 25 mm/sec. A P Atrial potential

are contracting efficiently in the latter beats. These observations might indicate, therefore, that the insignificant changes in intracardiac pressures recorded during this experimental condition are achieved only because of a maintained homeometric autoregulation of the cardiac performance. The increased force of contraction of the ventricle made possible by this mechanism must, therefore, reduce the cardiac reserve.

Summary and conclusions

Experimental ventricular pre-excitation was produced in 30 dogs, and ventricular pressures, aortic blood flow, and myocardial segment length were continuously recorded.

The following conclusions were reached:

1. Alternating pre-excitation produces profound changes in intracardiac pressures and blood flow and affects the contractility of the heart muscle. These beat-to-beat changes are compensated by the heterometric autoregulation of the heart.

2. The hemodynamic disturbances during a long run of pre-excitation are slight because of an autoregulatory mechanism of the homeometric type.

3. The presence of these two types of autoregulations seem to be demonstrated in these experiments without any change in heart rate, venous return, or outflow resistance, the parameters which are usually found to be altered when the role of these regulatory mechanisms of cardiac performance are studied. Our only variable is the number of efficiently contracting myocardial fibers due to the asynchronization of ventricular contraction.

We are indebted to Mr. Yonah Mahler, electronics engineer, and Mr. Shmuel Werkson for their help and assistance.

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A simple test of speed of response of electrocardiographs

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Recent work has shown that electrocardiograms obtained from direct writers of the hot stylus type may be subject to distortion sufficient to produce errors of interpretation.[1] It was found that under ordinary clinical conditions the performance of electrocardiographs could fall very far short of their manufacturer's specifications. For this reason it would appear desirable to have a simple means of testing the speed of response of an instrument. The means suggested in this communication involves a simple circuit and test procedure.

Method

The circuit of the E.C.G. tester is given in Fig. 1. By means of this circuit it is possible to inject into an electrocardiograph either a step of 1 millivolt or a 1 mv. exponential pulse or spike having a time-constant of 6.3 milliseconds. Because of the short duration of the pulse its full amplitude is not recorded by a direct writer. The recorded height of the pulse expressed as a percentage of the recorded height of the step gives an indication of the recorder's response to high frequency signals.

Procedure

The direct writer under test is attached as shown in Fig. 1 and the lead selector switch is turned to Lead I. The instrument is adjusted to any convenient sensitivity and buttons *A* and *B* are pressed alternately so that a short succession of square and spiked wave forms is obtained (Fig. 2). The ratio between the heights of the spike and square wave forms is expressed as a percentage and called the *percentage spike response*. During this procedure the accuracy of the internal 1 mv. calibration signal can be checked against the 1 mv. signal injected by the tester.

Results

The relationship between the percentage spike response and the cutoff frequency for some direct writers is shown in Fig. 3. For a set of 42 precordial electrocardiographic signals from children, recorded on magnetic tape and played back through

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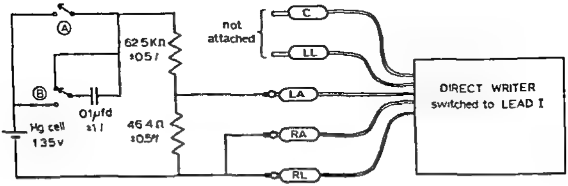

Fig. 1. Circuit of proposed tester and the method of attachment to an electrocardiograph.

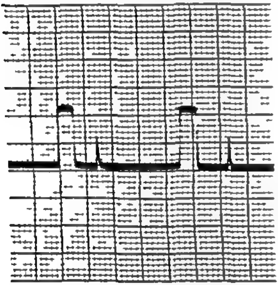

Fig. 2. The step and exponential spike pulse resulting from pressing buttons I and II of the tester diagrammed in Fig. 1 as they appear on a direct writer tracing. The ratio between the heights of the two signals is the spike response and provides an indication of the speed of response of the direct writer.

the same direct writers, the root mean square (RMS) errors are plotted against percentage spike response in Fig. 4. The method used in this procedure to obtain RMS errors was identical to that prescribed in a previous communication.[1]

A direct writer analog

It is apparent from Fig. 3 that there is a correlation between the spike response and cutoff frequency, so that a given spike response indicates a certain range of cutoff frequencies. To obtain a calibration, defining the center of this range, as well as to fill the gaps evident in Fig. 3, an analog circuit approximately representative of direct writers was devised. The design considerations of such a circuit are as follows.

The principal factors affecting the frequency response of a direct writer are the mechanical and electrical characteristics of the galvanometer, but the response also depends upon pre-emphasis networks and RC low pass filters if these are used. In spite of variations in internal structure, most direct writers have characteristics which are essentially flat within the pass band and then fall off initially with a slope approaching −18 decibels per octave. This suggests that a third-order low pass system may be a suitable analog. A current-driven galvanometer behaves as a second order spring mass system with an undamped natural frequency, f, dependent upon the inertia and spring constant, and a damping ratio, ζ (zeta), dependent upon the friction

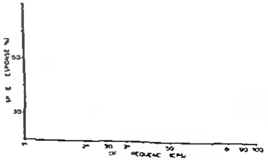

Fig. 3. Experimental measurement of the relationship between percentage spike response and frequency of some direct writers.

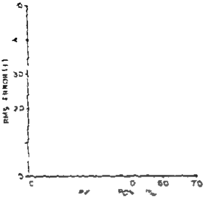

Fig. 4. Relationship between amplitude error in 42 tape recorded ECG signals expressed as percentage root mean square (RMS) error and spike response.

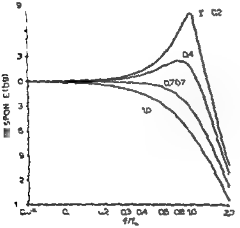

Fig. 5A. Deriving an analog for a direct writer. Response curves of second-order systems for various values of ζ.

and inertia. A third-order system may be considered to be an equivalent galvanometer current driven through a first-order lag network of suitably chosen time constant τ. Fig. 5A shows response curves of second-order systems for various values of the parameter ζ and Fig. 5B shows the response curves of a lag network to the same frequency scale for various values of $2\pi f_n\tau$. A third-order system will have a response which is the composite response derived from a pair of the curves A and B. By trial and error various values of ζ and $2\pi f\tau$ were used in an attempt to find a third-order response typical of direct writers. The most satisfactory fit was obtained using $\zeta = 0.707$ and $2\pi f\tau = 2$ (Fig. 5C). A comparison of the composite characteristic with response curves from 31 direct writers is shown in Fig. 6. Note that the actual cutoff frequencies are irrelevant in this comparison; each curve is shifted to obtain the best fit. Insofar as frequency response is concerned, the third-order system proposed should provide reasonable simulation of a direct writer when programmed on an analog computer.

By suitable variations of its time constants the above-described analog provided the equivalent of a typical direct writer whose frequency response curve could be shifted to the left or to the right to obtain a calibration curve for the proposed tester relating the percentage spike response and cutoff frequency (Fig. 7). In fact, this curve was obtained by varying the time-constant of the tester rather than the time scale of the analog. Fig. 7 also shows the points obtained by direct experimental measurement on actual electrocardiographs (Fig. 3), and their agreement with the analog curve is seen to be

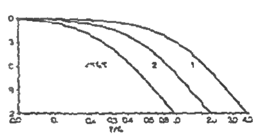

Fig. 5B. Response curves of a lag network for various values of $2\pi f\tau$.

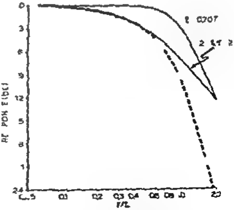

Fig. 5C. Response curve (*broken line*) of the third-order system derived from combining the responses for $\zeta = 0.707$ and $2\pi f\tau = 2$.

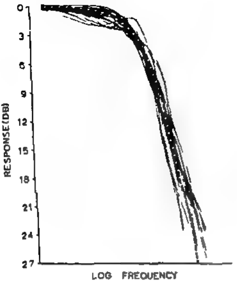

Fig 6 Thirty one direct writer frequency response curves superimposed on curve Fig 5C

quite close The asymptotes of the curve lie at 0 per cent and 100 per cent and there is a point of inflection at approximately 50 per cent and 50 c p s With the time constant used in the tester (6 3 milliseconds) the graph is approximately linear between 25 and 100 c p s which is the usual cutoff range of direct writers In addition the slope and therefore the accuracy of the indication is greatest in this range however a useful indication of cutoff frequency can be obtained up to 500 c p s

Discussion

There is no standardization of the method of specifying the speed of response of electrocardiographs[1] Einthoven used the deflection time or rise time to indicate speed of response and this had the merit of requiring no additional equipment However at paper speeds normally used a sufficiently accurate measurement of rise time cannot be made The response of an instrument is more accurately described by its frequency response curve If a single point on such a curve is to be used to provide a figure of merit it is conventional engineering practice to take the 3-db or half power point At this point the amplitude of the response is 70 7 per cent of the maximum low frequency response The frequency at this point is termed *the upper cutoff frequency*[2] Unfortunately there is no simple relationship between the rise time and the cutoff frequency but it is roughly given by (rise time between the 10 and 90 per cent points) × (cutoff frequency) = 0 35 to 0 45 with the exact value depending upon the system[3] The system in this case is considered to be accurately represented by the analog circuit described above The rise time of the analog was found to be 0 0071 sec in real time With a cutoff frequency of 50 c p s this gives a product of 0 35 for a typical direct writer The minimum requirements recommended by the Council on Physical Medicine and Rehabilitation of the American Medical Association imply a cutoff frequency of approximately 50 c p s[1]

It would be a convenience and involve no loss in generality if in addition to other requirements the specifications of an electrocardiograph were to include the percentage response to a pulse of a particular time constant Because of the simplicity of the association of a 50 per cent response with a 50 c p s cutoff frequency it is suggested that a time constant of 6 3 milliseconds is appropriate for this purpose If the manufacturers incorporated in their instruments a circuit such as that shown in Fig 1 and specified the percentage spike response of each instrument when properly adjusted it would be possible to include the spike pulse with the standard 1 mv calibration signal on routine tracings In this way the interpreter would have in front of him an immediate indication of whether the instrument was operating

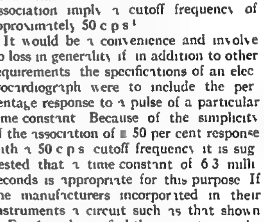

Fig 7 Employing the analog derived in Fig 5 the relationship between spike response and cutoff frequency has been plotted as a continuous cu[rve] Unselected experimental values for 1? direct

correctly not only with regard to its sensitivity but also with regard to its frequency of response

It should be pointed out that gross under damping could give an improved spike response and yet lead to considerable distortion The current practice of specifying that the overshoot in the response to the 1 mv direct current signal should not exceed 5 per cent or 0 5 mm at standard sensitivity should of course be retained With this proviso the spike response can provide a useful indication of an instrument s performance

A further claim in support of the use of the response of an instrument to an exponential pulse rather than its response to a sinusoidal signal can be made on the grounds that such a pulse more closely resembles the wave form to which the recorder would normally be responding The frequency response of some electrocardiographs depends to some extent upon the temperature of the stylus which in turn can be affected by the writing speed Hence a stylus which has been caused to swing from side to side over the surface of the paper may have a responsiveness which is different from that prevailing when a straight line is inscribed For this reason the frequency response curve of an instrument might conceivably give rise to a somewhat false impression of its performance as an electrocardiograph This difficulty is avoided when the spike response is employed

Summary

A convenient test of the speed of response of an electrocardiograph can be provided by a very simple circuit This provides an exponential pulse with a time constant of 6 3 milliseconds and an equal voltage step For a direct writer which barely meets the minimum requirements of the American Medical Association the recorded amplitude of the pulse is approximately 50 per cent that of the step If the tester is incorporated in the conventional calibration circuit only a capacitor and a button switch need be added

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Experimental pulmonary embolism and arteriosclerosis Effect of vasospasm

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Pulmonary vascular occlusion and arteriosclerosis have been experimentally produced by the intravenous injection of human blood clots[1] autologous fibrin and plastic beads[2] The emboli became incorporated into the intima of the vessels various stages of organization followed resulting ultimately in fibrous intimal thickening The lesions produced were localized and did not simulate the human counterpart In a preliminary communication Nityanand and associates[4] observed that fibrin given intravenously along with adrenaline produced more vascular occlusions and more widespread intimal thickening than did either given alone The results indicated that vasospasm of pulmonary vessels plays an important role in the production of experimental pulmonary embolism and arteriosclerosis In the present investigation a detailed study of the effect of vasospasm on pulmonary occlusion has been made Fibrin was used to produce emboli vasospasm was initiated with adrenaline as well as with serotonin whose vasoconstrictor action is 25 times that of adrenaline[5]

Harrison[1] studied the time taken to produce vascular occlusion after the injection of fibrin into the pulmonary circulation and observed that marked vascular occlusions occurred immediately but the number of these lesions decreased after 24 to 48 hours This finding was later confirmed by Barnard and Heard[6] Recently Springate[7] counted the number of fibrin emboli immediately after injection and 4 hours later and reported that 90 per cent of blood emboli disappeared from the lungs at the end of 4 hours These workers suggested that the disappearance of emboli was due to the fibrinolytic activity of plasma which played a major role in dissolving the intravascular deposits of fibrin Therefore it was thought to be of interest to study in the present investigation the fibrinolytic activity after intravenous injection of fibrin adrenaline and serotonin

Material and methods

Animals Thirty three male rabbits (average weight of 2 0 kilograms) of the C D R I colony were used They were given a standard diet of bran and green vegetables with water and were caged separately

Preparation of emboli The fibrin to be used as emboli was prepared by the modified technique of Barnard Forty five milliliters of blood was collected in oxalated tubes from the marginal ear vein of 3 rabbits which were used only for this purpose The plasma was separated and distributed equally in six tubes Undiluted plasma with a drop of thromboplastin was recalcified at 37°C to produce fibrin clot

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The fibrin fragments were washed several times with normal saline until colorless and were ground in a mortar to 1 mm size. The ground fibrin diluted in 10 ml of normal saline was injected slowly into the marginal ear vein of the rabbit with a No. 23 needle. Arterial spasm was produced by the intravenous injection of adrenaline chloride (May and Baker) 30 μg per kilogram of body weight and serotonin 200 mg per kilogram of body weight, both diluted with 1 ml of saline.

Planning of experiments. Experiment I was planned to study the histopathologic changes produced in the different groups and Experiment II was conducted to study the fibrinolytic activity of the plasma (see Tables I and II).

Histopathologic techniques. The animals of Experiment I were sacrificed by giving them magnesium sulfate intravenously 2 weeks after the last injection. Complete autopsy was performed on each animal. The lungs were inflated in situ with 10 ml of 10 per cent formol saline which was injected through the trachea. The intact heart and lungs were later fixed in the same solution. Five transverse blocks of the left lung at different levels and one longitudinal block from the right were taken, processed, and embedded in paraffin. Sections of 5 μ thickness were cut and stained with hematoxylin and eosin, Verhoeff's iron hematoxylin for elastic tissue, Heidenhain's azocarmine aniline blue for fibrin and collagen, and Von Kossa's silver nitrate for calcium.

Assessment of pulmonary lesions. The assessment of pulmonary lesions and the calculation of the embolic and arteriosclerotic indices were carried out according to the methods of Nityanand and associates.[4] For the determination of these indices in each animal one longitudinal and one transverse section of lung passing through the mid hilum region were stained with hematoxylin and eosin and examined under 6X eye piece and one third objective

Table I

Group	Material injected	Number of animals	Schedule of injection	Total injection	Time of sacrifice	Embolism
I	Saline	6	Biweekly	6	15 days after the last injection	−
II	Fibrin	6	Biweekly	6	15 days after the last injection	+
III	Adrenaline	6	Biweekly	6	15 days after the last injection	−
IV	Fibrin plus adrenaline	6	Biweekly	6	15 days after the last injection	+
V	Fibrin plus serotonin	6	Biweekly	6	15 days after the last injection	+
VI	Normal	3	—	—	15 days after the last injection	−

Table II. Various groups of Experiment II on which fibrinolytic activity was performed at 0, 1 and 24 hours

Group	Material injected	Number of animals	Number of injections
I	Saline	6	1
II	Fibrin	6	1
III	Adrenaline	6	1
IV	Fibrin plus adrenaline	6	1
V	Fibrin plus serotonin	6	1

Fig 1 Section of lung showing partial occlusion of a small pulmonary artery The animal received injections of fibrin and serotonin (Hematoxylin-eosin ×130)

of the microscope The number of normal arteries and those which showed evidence of embolism and intimal thickening were counted separately and the percentage ratio of pathologic to total arteries was expressed as *Embolic Index* and *Arteriosclerotic Index* respectively *

Plasma fibrinolytic activity Plasma fibrinolytic activity was determined on oxalated plasma by Mole s technique as modified by Srivastava and associates [8] Plasma 0 1 ml diluted with 0 8 ml of saline was clotted by the addition of 0 1 ml of M 40 $CaCl_2$ solution the final volume of the mixture being 1 0 ml After 24 hours of incubation at 37 C the extent of lysis of the fibrin clot was determined by aspirating with a tuberculin syringe all the fluid produced and measuring its volume Fibrinolytic activity was expressed as the volume percentage of the 1 0 ml clot that was liquified in 24 hours

Results

Experiment I

MACROSCOPIC APPEARANCE In Groups I II III and IV none of the animals died during the experiment whereas in Group V 2 animals died after the second injection The cause of death could not be ascertained Gross examination of the lungs revealed no abnormality in any of the groups There was no emphysema consolidation or infarction The heart appeared to be normal

Fig Section of lung showing large fibrin embolus causing destruction to the medial wall of a large pulmonary artery The animal was subjected to injections of fibrin combined with serotonin (Hematoxylin-eosin ×90)

$$\text{Embolic Index} = \frac{\text{All arteries showing embolism}}{\text{Total number of arteries}} \times 100$$

$$\text{Arteriosclerotic Index} = \frac{\text{All arteries showing intimal thickening}}{\text{Total number of arteries}} \times 100$$

Fig 3 Section of lung showing polypoid fibrin embolus at the lower end of a medium sized pulmonary artery The animal was subjected to injection of fibrin and serotonin (Hematoxylin-eosin ×90)

MICROSCOPIC APPEARANCE Groups II IV and V showed fibrin emboli incorporated into the intima at various stages of organization The smaller and medium sized vessels were obliterated by the fibrin emboli and were the main target of pathologic changes In the bigger vessels only the intima was thickened Smaller arterioles showed arteriolitis The lung parenchyma was normal In Group III the injection of adrenaline alone produced marked hypertrophy and corrugation of the internal elastic laminae only The most marked characteristic changes were seen in Group V In Group I there were no changes

ADDITIONAL DESCRIPTION OF EFFECT OF FIBRIN AND SEROTONIN The animals developed (a) fibrin emboli in the pulmonary arteries which caused vascular occlusion and organization that led to intimal thickening (b) arteritis and changes in the arterial walls and (c) alveolar phagocytic reaction

Fibrin emboli The fibrin emboli were obliterated, partially or completely in arteries of different sizes (Figs 1 3) These adhered to the wall of the arteries became partly organized at the site of attachment and endothelium grew over them In bigger arteries the fibrin emboli were incorporated into the wall at more than one place (Fig 4) The emboli after organization shrank and made the lumen irregular (Fig 5) In the organization of fibrin emboli all stages were seen (Figs 2 5 and 6) The recent emboli had a cellular response of macrophages fibroblasts and foam cells whereas older emboli showed an advanced stage of organization with proliferation of connective tissue and vascular neoformation The internal elastic lamina was not preserved in many arteries and changes in the media were seen (Fig 7) The changes were found in arteries of all sizes In some of the arteries there was focal or diffuse hyperplasia of the endothelium which could be seen in the

Fig 4 Section of lung showing a large pulmonary artery with two fibrin emboli incorporated on the left side of the vessel endothelium grew over them The animal received injections of fibrin and serotonin (Hematoxylin-eosin ×120)

Fig 5 Section of lung showing three organized emboli at three different places in a large pulmonary artery The animal was subjected to fibrin and serotonin (Hematoxylin-eosin ×90)

vessel wall In bigger vessels fibrous intimal thickening ecentric or focal was observed (Fig 8)

Changes in arterial walls Changes in the walls were seen in arteries of all sizes In small and medium sized vessels the internal elastic lamina appeared to be reduplicated triplicated and corrugated due to spasm the muscular part looked robust and the lumen of the vessel was small (Fig 9) In elastic vessels also there was reduplication of internal elastic laminae and breaking of elastic tissue which was replaced by reticulin (Fig 10) The acute and chronic inflammatory cells infiltrated both the intima and the media of some of the vessels which also had swollen endothelial cells The arterioles of the lung parenchyma were engorged with blood and showed perivascular cuffing by inflammatory cellular exudate formed of polymorphonuclear leucocytes lymphocytes and macrophages mixed with a variable amount of erythrocytes (Fig 11) The lung parenchyma showed no exudate or infarction except the changes in blood vessels already described

Alveolar phagocytic reaction There were inflammatory cells in the septa or alveoli They were different from arteriolitis for no red blood cells could be seen in the exudate

A comparison of the extent of the lesions of the pulmonary vessels in different groups is shown in Table III It is evident that the lesions of the pulmonary arteries in the fibrin plus adrenaline group are the same as in the fibrin plus-serotonin group The number of vascular occlusions is much greater in the fibrin plus serotonin group than in any other group In the serotonin plus fibrin group all types of lesions were seen in arteries of all sizes whereas the adrenaline plus-fibrin group showed lesions in small and medium sized arteries

Experiment II

The mean values of plasma fibrinolytic

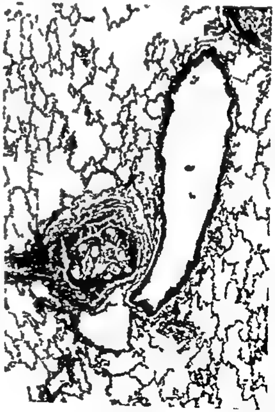

Fig 6 Section of lung showing almost complete occlusion of a small pulmonary artery by organizing embolus The animal received injections of both fibrin and serotonin (Hematoxylin-eosin ×90)

Fig 7 Section of lung showing all stages of organizing embolus in a large pulmonary artery Changes were seen in the media The animal was subjected to injections of fibrin and serotonin (Hematoxylin eosin ×90

activity observed at various intervals are given in Table IV

In Group I the fibrinolytic activities at 0 hour 1 hour, and 24 hours were the same whereas in Groups II III, IV and V there was a significant increase in the plasma fibrinolytic activity at 1 hour but in all these groups the fibrinolytic activity came back to the normal level at 24 hours

Discussion

From clinical evidence it has been suggested that repeated emboli in the pulmonary circulation cause vascular occlusions intimal fibrosis and hypertension leading to cor pulmonale In the case of massive pulmonary emboli most of the pulmonary circulation is cut off there is no infarction and death follows rapidly due to right ventricular failure In the case of minute pulmonary emboli no abnormality in the lungs can be recognized by macroscopic examination but histologic section shows that many small arteries are wholly or partially occluded by fibrous intimal thickening Organizing fibrin network which causes obstruction is found Over the years this causes a rise in pressure in the pulmonary circulation

It is known that generalized vasospasm associated with pulmonary thromboem

Fig 8 Section of lung showing two big pulmonary arteries The left pulmonary artery shows thickening of the intima in the lower part The right pulmonary artery shows marked fibrous thickening of the intima at the site of branching The animal was subjected to injections of fibrin and serotonin (Hematoxylin-eosin ×90

Fig. 9. Section of lung showing markedly thickened media of a small pulmonary artery with an intense corrugation of the internal elastic lamina. The animal was subjected to injections of fibrin and serotonin. (Verhoeff's iron hematoxylin stain. ×90.)

Fig. 10. Section of lung showing elastosis of large pulmonary artery. The animal received injections of fibrin and serotonin. (Verhoeff's iron hematoxylin stain. ×400.)

Table III. Number of pulmonary arteries showing pathologic changes as compared to normal

Group	*Normal*			*Embolism*			*Intimal thickening*	*Total number of arteries*	*Arterio-sclerotic index†*	*Embolic index†*
	Big	*Medium*	*Small*	*Big*	*Medium*	*Small*				
Fibrin										
L	7	10	42	1	[illegible]	1	14	[illegible]7	18.0	5.38
T	9	13	43	2	3	5	27	98	27.25	6.1[illegible]
Adrenaline										
L	3	21	40	0	0	0	[illegible]	114	[illegible]	0
T	2	9	37	0	0	0	0	73	0	0
Fibrin plus adrenaline										
L	[illegible]	[illegible]	1[illegible]	6	2	8	47	92	51.08	18.47
T	[illegible]	[illegible]	[illegible]8	4	[illegible]	[illegible]	48	106	45.[illegible]8	15.09
Fibrin plus serotonin										
L	[illegible]	[illegible]	1[illegible]	4	9	[illegible]	41	89	46	15
T	4	13	[illegible]	10	[illegible]	8	24	[illegible]3	34	34

*These are the same groups described previously by Nityanand.

†For Embolic Index and Arteriosclerotic Index, see footnote on page 531.

bolism is an important factor in the development of clinical arteriosclerosis and hypertension.[9] In the present experiments the injection of adrenaline, a known pulmonary vasospasmodic,[10] alone or with

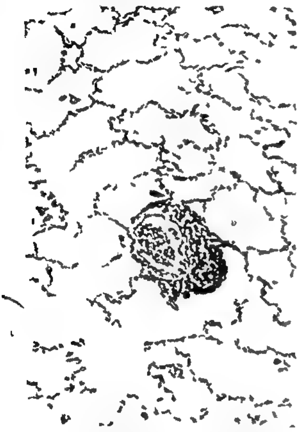

Fig. 11. Section of lung showing perivascular lymphocytic cuffing of an arteriole containing red blood cells. The animal had been given repeated injections of fibrin and serotonin. (Hematoxylin eosin. ×710.)

fibrin emboli into the marginal ear vein of rabbits caused lesions which were more widespread and greater in number in small than in medium-sized arteries, whereas repeated showers of fibrin emboli along with serotonin produced vascular occlusions in vessels of all sizes followed by eccentric intimal fibrosis. The vasospasm due to serotonin possibly interfered with intimal nutrition and therefore the circumferential lesions consisted not only of fibrosis but also of elastic tissue. The changes in the walls of the bigger vessels with eccentric layers of elastic tissue and collagen fibers are also suggestive of sustained arterial hypertension. Barnard[10] found the same type of lesions in rabbits which had been killed 5 months after the thirty-fifth injection of blood clot.

The embolic phenomenon in vessels of all sizes was marked in the serotonin plus fibrin group and the lesions were seen in arteries of all sizes. This may be due to the fact that serotonin causes a much higher and more sustained rise in pulmonary pressure than does adrenaline.

The number of affected pulmonary vessels was almost the same in the fibrin plus adrenaline group as in the fibrin plus serotonin group but was definitely greater than in the fibrin group. The animals which received adrenaline showed spasm of the medium and small-sized arteries but there was no evidence of degeneration or necrosis of the plain muscle of the arteries. Constantinides and associates[11] reported that injections of adrenaline in animals caused

Table IX. Mean values of plasma fibrinolytic activity at various intervals

Group	Number of animals	Actual mean values with standard errors			Changes from initial value (mean values with standard errors)	
		Initial (0 hr.)	1 hr.	24 hr.	0 to 1 hr.	0 to 24 hr.
Control	6	54.5 ± 0.76	55.2 ± 0.88	54.2 ± 0.92	+ 0.7 ± 1.02	+0.3 ± 1.07
Adrenaline	6	58.5 ± 0.76	76.7 ± 0.88	56.0 ± 0.92	+18.2 ± 1.02	−2.5 ± 1.07
Fibrin	6	53.5 ± 0.76	68.3 ± 0.88	52.0 ± 0.92	+14.8 ± 1.02	−1.5 ± 1.07
Adrenaline plus fibrin	6	53.5 ± 0.76	72.8 ± 0.88	53.3 ± 0.92	+19.3 ± 1.02	−0.2 ± 1.07
Serotonin	6	52.3 ± 0.53	73.1 ± 0.63	55.4 ± 0.52	+20.8 ± 0.69	+1.1 ± 0.49

Note: The standard errors for each measurement have been based on the pooled estimate of the variance from the four treatment groups—on 20 degrees of freedom, since the variances have been found to agree very well.

advanced necrosis of the aortic wall without producing any change in the coronary arteries. This may be due to the fact that adrenaline has a vasospasmodic effect on visceral arteries and causes toxic medial degeneration in peripheral arteries. Further experiments will have to be made before any definite conclusions can be drawn.

The occurrence of arteriolitis and acute arteritis during experimental pulmonary thromboembolism has been described by Tamayo and associates.[1] It has been suggested that this may be due to pulmonary hypertension but in the present investigation the animals which had been given adrenaline alone failed to show any such lesions whereas these lesions were present in the animals which had been given injections of fibrin. Hence it appears that fibrin is related to the development of arteriolitis.

No pulmonary infarction was observed in spite of the occlusion of the vessels. This may be due to the fact that the lung of the rabbit has more collateral circulation than that of man and the bigger vessels were never obliterated completely enough to hinder the circulation. Further studies will be necessary before any opinion can be expressed. Sepaha and associates[13] did not find any evidence of pulmonary infarction in dogs who had weekly injections of autoclots.

Springate[7] observed that emboli of blood clots or fibrin which were used to produce experimental pulmonary embolism were lysed and only a small number was left to be organized. Harrison[1] noted that the lesions were much less severe in animals which were sacrificed several months after the last injection. After embolization of a single large thrombus formed in an isolated vein after intravenous injection of 30 ml of heterologous thrombus free canine serum eluate Wessler[4] observed marked reduction in the volume of the emboli during the first 2 weeks. It is believed that in the normal circulation minute fibrin thrombi are continually formed and deposited on the endothelial wall of blood vessels and that these thrombi are dissolved by the fibrinolytic activity of the plasma[14] but under pathologic conditions this fibrinolytic activity increases. In the present investigation fibrinolytic activity increased markedly perhaps as a defense mechanism in an attempt to lyse the exogenous fibrin. This defense mechanism was limited in its effect as was evident from the fact that the activity increased at 1 hour but came back to normal within 24 hours. This could explain the necessity of repeated injections of fibrin to produce widespread arteriosclerosis in the lungs.

Summary

1 Pulmonary embolism was produced in rabbits by repeated intravenous injections of homologous fibrin adrenaline and serotonin.

2 Pulmonary arteriosclerosis and occlusion were observed in arteries of all sizes. The embolic index was higher in the serotonin plus fibrin group than in the adrenaline plus fibrin group.

3 Vasospasm produced by drugs definitely plays an important role in the production of experimental pulmonary lesions.

4 Plasma fibrinolytic activity was studied in 30 rabbits at 0 hour 1 hour and 24 hours after the intravenous injection of fibrin adrenaline and serotonin singly or in combination. It was observed that plasma fibrinolytic activity increased markedly 1 hour after the injection and returned to normal after 24 hours in all groups except the control.

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Case reports

Anomalous venous drainage of the left lung into the inferior vena cava

A case report

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Anomalous pulmonary venous drainage into the right side of the heart may be total or partial. It is considered to be total if the anomaly involves all pulmonary veins of both lungs, and partial if the abnormal venous drainage involves the whole or part of one lung or, rarely, part of both lungs. Partial anomalous pulmonary venous drainage of the right lung is more frequently encountered than that of the left. When anomalous drainage involves all or some of the left pulmonary veins, the abnormal connection is generally into a supradiaphragmatic site such as the left innominate vein, left superior vena cava, left subclavian vein, or coronary sinus. The following case is, to our knowledge, the first reported instance of anomalous pulmonary venous drainage of the entire left lung into the inferior vena cava.

Case report

S. W., a 6-year-old Negro girl, had had frequent attacks of cough and fever, usually lasting for a few days, over the last several years. In January, 1963, she developed fever and cough which persisted for several weeks and which subsided with penicillin therapy. At this time a systolic murmur was heard at the base of the heart, and she was referred to the cardiac service for cardiac evaluation.

Physical examination revealed a normally developed and nourished child who weighed 48 pounds. There was no respiratory distress, no cyanosis, and no clubbing of the digits. The left hemithorax appeared to have slightly lesser expansion than the right during normal respiration. On palpation the trachea was centrally situated. Auscultation of the lungs was normal. The cardiac apical impulse was displaced to the left, being close to the anterior axillary line in the fifth left intercostal space. There was no thrill and no precordial heave was observed. The second heart sound was normal in intensity and normally split. A Grade 2/6 to 3/6 systolic ejection murmur was heard maximally at the second left intercostal space. The rest of the physical examination was within normal limits.

An x-ray film of the chest (posteroanterior projection) revealed a marked shift of the heart toward the left (Fig. 1). The cardiac contour in the right anterior oblique projection was not unusual. In the left anterior oblique projection the anterior cardiac border lay farther from the anterior chest wall, whereas the posterior cardiac border easily overlapped the spine. The left hemithorax seemed to be somewhat smaller than the right, and the translucency of the right lung appeared to cross the midline. The electrocardiogram revealed regular sinus rhythm, frontal QRS axis of +90 degrees, P-R interval of 0.13 second, and QRS interval of 0.07

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Fig 1 Posteroanterior chest roentgenogram demonstrating leftward shift of the heart

second There was no definite evidence of hypertrophy of the chambers The QRS complexes over the right precordial tracings appeared to be relatively small The electrocardiogram was interpreted to be within normal limit On bronchoscopy the carina was blunt and the left main bronchus was stenotic and edematous The distal branches of the left bronchus could not be visualized Bronchography demonstrated narrowing of the left main bronchus and a hypoplastic irregularly narrowed left bronchial tree (Fig 2)

Angiocardiography with injection of dye into the right atrium confirmed the marked leftward displacement of the heart accompanied by some posterior rotation of the cardiac apex in the horizontal plane The latter was demonstrated by the unusual posterior location of the left ventricle and interventricular septum in the lateral projection There was no evidence of an intracardiac shunt The pulmonary arterial tree of the left lung appeared to be somewhat hypoplastic In the levoangiocardiogram no left pulmonary veins were seen to drain into the left atrium Instead in the left lower lung field two blood vessel appeared which seemed to unite into a relatively large common trunk in the region of the left cardiophrenic angle which proceeded horizontally to the midline where it overlapped the aorta These vessel opacified at the same time as the chambers on the left side of the heart and the aorta and were then considered to be probably aberrant systemic arteries (Fig 3) However aortography performed a few days later failed to demonstrate the abnormal vessels in the left lung field A tentative diagnosis of hypoplasia of the left lung with possible associated pulmonary sequestration involving the left lower lobe and secondary leftward displacement of the heart was made

Exploratory thoracotomy revealed that the left lung was diminutive No interlobar fissure was present A rather small pulmonary artery was observed to enter the left lung at its hilum but no pulmonary vein could be found in its usual location

Fig 2 Bronchogram showing narrowing of the distal left main bronchus and hypoplastic appearance of the left bronchial tree

Fig. 3 A Levoangiocardiogram in the frontal projection (6 seconds) showing the opacified abnormal vessel from the left lung (*see arrow*) Note normal pulmonary venous return from the right lung *B* Lateral angiocardiogram showing two anomalous pulmonary veins converging into a single trunk (*see arrows*)

However, the entire left lung was found to drain into a single pulmonary vein which emerged in the inferior pulmonary ligament and passed through the diaphragm near the midline. There was no arterial supply to the left lung from the aorta. The anomalous pulmonary vein was noted to contain dark venous-like blood which suggested that presumably the left lung participated only to a small degree in respiratory gas exchange. The anomalous vein was ligated just above the diaphragm and the left lung was removed. The postoperative course was uneventful.

When the angiocardiogram was viewed in retrospect, it was evident from the horizontal course of the anomalous pulmonary vein that it very likely drained into the inferior vena cava. Since blood issuing from this vein was observed to be venous-like rather than arterial, it is conceivable that a significant step-up in oxygen saturation would not have been detected at the site of entrance of the anomalous vein into the inferior vena cava or at the right atrium had cardiac catheterization been performed.

Comment

Brody[1] in 1942 collected from the literature a total of 102 cases of anomalous pulmonary venous drainage. Excluding all cases of total anomalous pulmonary venous drainage, anomalous drainage of the whole left lung was present in 10 cases, and of part of the left lung in 10 cases. A search of the Anglo-American literature since then has revealed 24 more cases[2-15] of drainage of the entire left lung into the right side of the heart, including some older references overlooked by Brody, and 11 more cases[4, 16-21] in which part of the lung (usually a variable extent of its upper lobe) drained anomalously. Six additional cases of left anomalous pulmonary drainage have been reported in which specific statement was not made whether part or whole of the left lung drained abnormally.[22-25] Of 51 cases of anomalous venous drainage involving only the left lung which were collected from the literature, including the 20 cases cited in Brody's paper,[1] the site of insertion of the anomalous pulmonary vein was the left innominate vein in 31 cases, the left superior vena cava in 14 cases, the coronary sinus in 2 cases, the left subclavian vein in 1 case, and the right superior vena cava in 1 case. In one case the anomalous left pulmonary veins drained into the left innominate vein and coronary sinus,[7] and in another case they were reported to have drained into the superior vena cava and left ventricle(?).

Occasionally, partial anomalous venous drainage of the left lung is associated with partial or complete anomalous venous drainage of the right lung and vice versa.[6, 30] Of 68 cases in which anomalous pulmonary veins drained into the inferior vena cava, collected from the literature, 8 were common pulmonary veins carrying the total pulmonary blood flow, whereas 60 were veins draining part or all of the right lung. We have been unable to find any previous instance of anomalous pulmonary venous drainage from the left lung into the inferior vena cava.

In recent years the existence of a syndrome wherein anomalous venous drainage of the right lung into the inferior vena cava is associated with a hypoplastic and often bilobed right lung, an abnormal right bronchial tree, and often an aberrant systemic arterial supply to the right lung has gained wide recognition.[31-34] It has been called the "scimitar syndrome"[33] and "vena cava bronchovascular syndrome."[26] The heart in this syndrome is usually displaced toward the right lung. The case we report here appears to be the first instance of a similar syndrome involving the left lung associated with displacement of the heart to the left.

Anomalous connections between systemic and pulmonary veins are assumed to be due to the persistence of connections in embryonic life between the primitive pulmonary vascular plexus, the splanchnic plexus, and the tributaries of the cardinal venous system. This is associated with failure of the pulmonary venous system to make connection with outpouchings from the sinoatrial region of the heart. It was pointed out by McCotter[16] and more recently by Neill[27] that anomalous pulmonary drainage into the left innominate vein, into the left superior vena cava, and into the coronary sinus are closely related variations of the same basic anomaly, differing only in the extent to which the left common cardinal vein remains patent. Partial anomalous venous drainage of the right lung is several times more common than that of the left. Total anomalous pulmonary venous drainage into the left innominate vein or left superior vena cava occurs more often than into the right superior vena cava. Shaner[28] suggested

that this may be related to the fact that in the embryo the left bronchial vein is a much more constant structure than the right It is much more likely therefore to drain all the pulmonary veins when the latter fail to establish connection with the left atrium It is uncommon for an anomalous pulmonary vein (excluding total anomalous pulmonary venous drainage) to cross the midline before it joins the receiving systemic vein as in our case This can happen however because the splanchnic vascular plexus which enters into the composition of a segment of the anomalous vein is essentially a midline structure

The paucity of positive physical signs in this entity can lead to its being easily overlooked The diagnosis may be suspected in cases in which the heart is shifted to the left side and the hemithorax on that side appears small in the absence of any obvious cause These abnormalities are best detected in routine chest roentgenograms Angiocardiography is indicated in such cases to visualize the abnormal pulmonary vein or veins The left to right shunt in cases such as ours with anomalous venous drainage of an entire lung into the inferior vena cava is probably less than half the total pulmonary flow This assumption is made because the hypoplastic abnormally draining lung presumably has a smaller flow than the other lung Anomalous drainage of one entire lung is compatible with longevity one patient with this condition lived to 86 years[11] Nevertheless these patients run the risk of being in serious trouble if the normal lung is affected by disease

Summary

Relevant anatomic details of previously reported cases of anomalous pulmonary venous drainage involving the left lung are briefly reviewed

A case of anomalous drainage of the entire left lung into the inferior vena cava is described It was associated with a hypoplastic left lung with absent interlobar fissure and shift of the heart to the left To our knowledge this is the first reported instance of such an anomaly

The operation in this case was performed by Dr John Raffensperger and Dr Milton Weinberg Jr and we are indebted to them for the surgical data

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Dissecting aneurysm of the carotid artery and aorta after carotid angiography

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The nature of the lesion if any in the wall of the aorta in dissecting aneurysm is controversial[1-3] The following case report is considered to be pertinent to the problem It constitutes as well a hitherto undescribed medical curiosity

Report of case

The patient was a 41 year-old white woman with a history of pulmonary tuberculosis who apparently had been successfully treated with chemotherapeutic agents 2 years prior to admission She was said to have had epilepsy as a child but had suffered no seizures since 1 year before admission grand mal seizures recurred followed by left hemiparesis Percutaneous carotid angiography revealed narrowing of an intracranial branch of the left internal carotid artery and he was placed upon anticonvulsant therapy One month before admission while at a chronic disease hospital she fell twice during grand mal seizures and struck her head on both occasions Four days prior to entry she had two grand mal seizures and reversal of plantar reflexes was noted bilaterally On the next day he developed fever A chest roentgenogram revealed a pulmonary infiltrate. There was peripheral blood leukocytosis and culture of the sputum yielded *Staphylococcus aureus* Multiple antibiotic agents were administered and the patient was transferred to the Cincinnati General Hospital

On admission he was comatose and febrile with rapid pulse and respirations Blood pressure was 135/ 0 mm Hg Evidence of pneumonia was detected on physical examination of the chest Major neurological findings comprised meningismus fixed pupils papilledema on funduscopic examination hyperreflexia and bilateral Hoffman and Babinski signs When a xanthochromic cerebrospinal fluid containing 8 000 crenated erythrocytes was obtained on lumbar puncture a craniotomy was performed A chronic subdural hematoma was evacuated from the left frontal temporal and parietal region Many blood pressure readings were recorded postoperatively and during her entire stay in the hospital with a range up to 140/110 mm Hg most diastolic level were above 90 mm Hg Over the next 3 days the patient seemed to be improving while receiving supportive and antibiotic therapy The fever disappeared and there was marked improvement in her sensorium motility and pupillary reactions Three days later he suddenly lapsed into coma but remained afebrile despite a persistent leukocytosis On the fourteenth hospital day the successful performance of left carotid angiography revealed slight displacement of the anterior cerebral artery to the right suggesting a minimal residual subdural hematoma. Three days later culture of material draining from the craniotomy wound yielded *Staphylococcus aureus* Despite intensive antibiotic therapy the initiation of a cardiac regimen and occasional blood transfusions the patient's condition continued to deteriorate By the twenty fifth day the patient was virtually moribund on that day left carotid angiography was again attempted The operator experienced great difficulty in gaining access to the vessel despite three attempts and the study was not completely satisfactory Roentgenograms revealed that the first injection was intramural the contrast medium extended from the lowermost cervical region inferior to the needle site to the carotid bifurcation (Fig 1) The thorax was not shown on

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Fig 1 Carotid angiogram which reveal intramural injection of the medium with extension to the carotid bifurcation above Below medium extends to the thoracic inlet lowest point visualized

the films The subsequent two injections revealed no intramural contrast medium On the following day the patient died

At necropsy the brain revealed a scant residuum of the chronic left subdural hematoma In addition there was diffuse purulent meningitis and a focal left subdural empyema both were caused by *Staphylococcus aureus* The heart weighed 370 grams and showed no significant abnormalities The lungs manifested widespread lobular pneumonia and focal bilateral active apical pulmonary tuberculosis In addition there was a fatty liver with focal nonspecific hepatitis the latter presumably related to sepsis

The findings of greatest interest were observed in the left common carotid artery and aorta At a point approximately 6 cm above the origin of the common carotid artery there were five minute complete perforations through the anterior wall There were three openings in the posterior wall these did not however pass completely through the wall but entered into it (Fig 2) The posterior half of the carotid artery was involved by a dissecting aneurysm which communicated with the lumen through the posterior needle holes (Fig 2) The dissection extended distally only to the bifurcation of the common carotid artery but proximally it entered the wall of the aorta totally dissecting the wall of the ascending segment and arch (Fig 3) The tract extended into the descending thoracic aorta for a distance of 8 cm here affecting approximately 50 per cent of the circumference There were neither internal nor external communications of the dissection tract with any structure other than the lumen of the left common carotid artery

Microscopic examination of the carotid artery at the point of perforation revealed a very recent

Fig 2 The specimen of the carotid artery and its branches reveal almost in the center minute perforations entering the dissection tract in the posterior wall The two apparent linear lacerations below proved to be artifactitious related to cannulation of the vessel during the autopsy examination Note the bulge in the posterior wall representing the intramural hematoma and ceasing just below the bifurcation

needle tract passing through the anterior wall of that vessel A similar tract entered the posterior wall from the lumen and contained partially clotted blood (Fig 4) The perforations were recent and compatible in appearance with a needle tract 1 day old

The elastica in the area revealed no intrinsic abnormality and the elastic tissue in the vicinity of the dissection tract in both the carotid artery (Fig 5) and the aorta (Fig 6) was similarly normal In both areas the outer third of the wall was affected by a recent dissecting aneurysm which was similar in age to that of the carotid needle tract

Discussion

The case described is of interest as a medical curiosity since we are unaware of any previous instance of dissecting aortic aneurysm complicating carotid angiography Infiltration of contrast medium along the carotid artery is said to be a frequent occurrence with carotid angiography [9] but it is uncertain whether this invariably represents intramural injection In some instances the radiopaque material may merely extend along the outer adventitia within the carotid sheath

On the other hand short dissections or intramural hematomas of the carotid artery are not rare after carotid angiography [9,1] Furthermore dissecting aneurysms of the aorta have been described after translumbar aortography [10,11] In these instances the volume of the dissection tract may in large part be accounted for by the quantity of contrast medium injected In the present case it seems clear that dissection by the blood originating in the lumen must have been the major factor since no more than 10 c c of contrast medium is ordinarily injected in cerebral angiography [8] Since intramural injection was observed only on the first attempt less than 10 c c of contrast medium gained access to the wall

The clear chronological association of recent carotid angiography with a fresh dissecting aneurysm affords strong evidence of a cause and effect relationship When there are added to this the observation of needle punctures communicating through the wall of the carotid artery with the dissection tract and the lack of any internal rupture elsewhere this hypothesis can scarcely be challenged It is also noteworthy that the carotid artery is uncommonly affected in spontaneous dissecting

Fig 3 Photograph of the entire thoracic aorta showing total dissection The white paper wedges denote the intramural hematoma Although there is mild atherosclerosis no aortic perforation is seen

Fig 4 One of the points of perforation in the carotid artery is depicted here The orifice enters the dissection tract within the wall (Hematoxylin and eosin stain ×60 reduced)

aneurysm Among 35 dissecting aneurysms studied at the Cincinnati General Hospital only 3 revealed significant extension into the common carotid artery in the neck although in many cases short segments of the carotid vessels were affected at their origins [7]

The case reported offers evidence for the concept that dissecting aneurysm usually originates in the lumen and penetrates the wall *It is of interest that the multiple* complete perforations of the anterior wall of the carotid artery had no significant effect on the integrity of the vessel whereas the incomplete perforations of the posterior wall *apparently initiated the dissection* The column of blood dissected readily through an apparently normal aortic wall The conclusion seems inescapable that any circumstance which permits the passage of blood *into* but *not through* the wall of a major blood vessel may initiate dissection No underlying medial disease need be postulated Hypertension of course may increase the likelihood of such an occurrence it is noteworthy that elevated diastolic blood pressures were frequently recorded in the patient reported on here

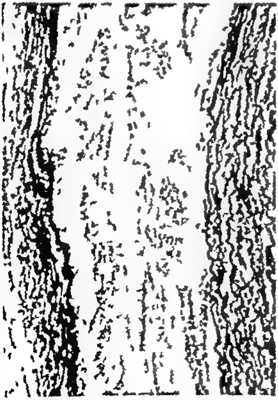

Fig 5 The dissection tract in the wall of the common carotid artery is shown in this photomicrograph The elastica is perfectly normal (Verhoeff van Gieson stain ×160 reduced)

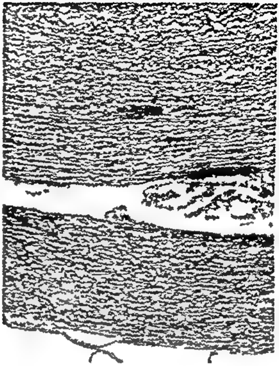

Fig *6* Normal elastica is seen adjacent to the aortic dissection tract The dissection occupies the characteristic location in the outer one third of the wall adventitia is above (Verhoeff van Gieson stain ×60 reduced)

Summary and conclusions

A dissecting aneurysm involving the posterior wall of the common carotid artery and the entire thoracic aorta originated from multiple needle perforations into the posterior wall of the carotid vessel at the time of angiography The walls of both the carotid artery and the aorta revealed no significant disease It is concluded that dissecting aneurysms may occur in essentially normal aortas when the luminal blood is permitted to gain access to the wall by an incomplete perforation

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Clinical pathologic conference

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Clinical abstracts

History. A 60 year old man suddenly became weak and sweaty while eating breakfast. He had no pain or dyspnea. His physician confined him to bed with the clinical diagnosis of acute myocardial infarction.

The patient had been well previously except for a gastroenterostomy for duodenal ulcer when he was 37 years old and an operation for obstruction of the small bowel when he was 44. There was no past history of chest discomfort, shortness of breath, or limited exercise tolerance. He took little alcohol and had smoked one package of cigarettes daily for many years. The family history was not remarkable.

On the seventh day after the episode of sweating and weakness, the physician stated that the patient developed acute left ventricular dilatation, a loud apical systolic murmur transmitted to the left axilla, and complete left bundle branch block. The patient now experienced congestive failure and gradually improved during the following weeks with digitalis and mercurial diuretics.

In the seventh week there was sudden, sharp chest pain which was intensified by deep breathing, a nonproductive cough, fever, and a recurrence of dyspnea and edema. The patient entered the hospital for the first time because of this relapse.

Physical examination. On examination the patient was thin and dyspneic and had moderate edema of the legs. The temperature was 100 F (37.8 C) rectally, the heart rate was 88 with an irregular rhythm, and the respiratory rate was 16. The neck veins were distended when the patient was at an angle of 45 degrees. The lungs were normal except for scattered crepitant basal rales. The cardiac impulse was heaving, and the point of maximal impulse was in the fifth intercostal space at the anterior axillary line. All examiners agreed that there was a loud (Grade 5/6) harsh pansystolic murmur, that there was no diastolic murmur, and that P_2 was much louder than A_2. Two examiners said the murmur was maximal at the apex, radiating to the axilla and toward the base. Two others stated that the murmur was maximal over the fourth and fifth intercostal spaces just to the left of the sternum, transmitted to the entire left chest, and that a thrill was present. The edge of the liver was firm and tender and was 6 cm. below the costal margin. The spleen was not felt. There was pitting edema of the ankles. The calves were normal without any evidence of peripheral venous or arterial abnormality.

The hemogram was normal. The urine had a specific gravity of 1.015. There was 1+ protein, occasional white and red blood cells, and a few granular casts and bacteria. The nonprotein nitrogen was 30 mg. per cent, and the serum electrolytes were normal. The ECG showed atrial fibrillation with QRS of 0.11 second. There was good evidence for anterolateral myocardial infarction of uncertain age and for left ventricular hypertrophy. A nonspecific intraventricular conduction defect was also present. Serial tracings revealed no significant change. X-ray examination of the chest showed generalized cardiomegaly, pulmonary congestion, and minimal fluid at the base of the right lung (Fig. 1). The fluoroscopist was impressed by the greatly enlarged left ventricle.

The patient was treated with digitalis, diuretics, and anticoagulants. The cough, fever, and edema improved promptly, and he was discharged after 6 weeks on a low salt diet, digitalis, and Dicumarol. He was followed for the next year in the outpatient department with his dyspnea and edema controlled by medication. He did not continue his work as a watchman.

A year after discharge and 18 months after the onset of his illness the patient was readmitted to the hospital because of pain in the upper abdomen and jaundice. He made an uneventful recovery after cholecystectomy and the removal of three large stones from the common bile duct despite the presence of bile peritonitis at the time of operation. During this hospitalization a diffuse precordial impulse was seen in the fifth and sixth intercostal spaces from 3 cm. to the left of the midclavicular line almost to the midaxillary line. The harsh

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Grade 5 pansystolic murmur was loude t in the fourth intercostal space at the left sternal border and was heard well at the apex and over the base After discharge from the surgical service the patient was not seen for the next 2 years

The patient s third and final adm ion $4\frac{1}{2}$ years after the onset of hi heart trouble was brought about by lower abdominal cramping of 1 month s duration not associated with any change in ga tro intestinal function and not related to either eating or bowel movement Upon adm ion hi temperature was 98 F (36 6 C) the pulse 60 and irregular the blood pre sure 110/65 mm Hg and the respira t ons were 18 per minute There was no change in the phy ical findings of the heart Except for an increase in amplitude of the complexes in the left precordial leads the electrocardiogram (Fig 2) wa much the same as those taken 4 years previously The chest x ray film showed a generalized cardiomegaly pulmonary congestion and right pleural ef fu ion The abdomen was mildly di tended the bowel sound were active and there was generalized tenderness rebound tenderne s and guarding No organs or masses were felt X ray films of the abdomen showed no definite evidence of obstruction The remainder of the physical examination wa normal except for moderate edema of the legs and sacrum

Laboratory data The urine had a pecific gravity of 1 015 1+ protein and contained Klebsiella and *Pseudomonas aeruginosa* on culture The hematocrit was 43 per cent the leukocyte count 16 500 and the serum electrolytes and blood urea nitrogen were normal

A laparotomy was performed on the day of ad mi sion Postoperatively there was progres ive orthopnea and dy pnea The edema increased bloody urine with fragments drained from the indwelling catheter and there were numerous loose stool The serum electrolytes and fluid balance could not be controlled satisfactorily The patient deteriorated progres ively suffering from dilutional hyponatremia mil l azotemia (blood urea nitrogen 35) and congestive circulatory failure He died on the twenty second postoperative day 4 years and 9 months after the original diagnosi of myocardial infarction

Fig 1 X ray film of the chest howing enlarged heart

Discussion

DR ROBERG The salient feature of this history is the abrupt onset of weakness and sweating complicated 7 days later by the sudden development of heart failure and a loud murmur For the first several months it was difficult to control the heart failure Then for the next 4^1 years his clinical status did not change One gains the impression that the patient suffered an acute physical insult to his heart and that the heart was able (with the assistance of digitalis and diuretics) to adjust satis factorily to an increased work load caused by this injury The patient tolerated an operation upon the biliary tract $1\frac{1}{2}$ years after his heart attack We can but guess how long he might have lived had he been spared the illness which led to the second abdominal operation

The onset was consistent with acute myocardial infarction On the seventh day the patient developed congestive failure and the physician observed (1) acute dilatation of the left ventricle (2) the development of a Grade 5 apical systolic murmur which radiated to the axilla and (3) ECG evidence of complete left bundle branch block The acute left ven tricular dilatation and heart failure and the loud systolic murmur allow only two diag noses to be entertained (1) rupture of a papillary muscle and (2) perforation of the interventricular septum Either acute mitral insufficiency or an acute left to right shunt would explain the left ventricular dilatation The complete left bundle branch block might statistically favor infarction of or dissection into the septum In a single patient with myocardial infarction left bundle branch block is not of precise localizing value I have mentioned dis section because ruptures of the septal or nonseptal aspects of the left ventric are not usually simple perforations thr

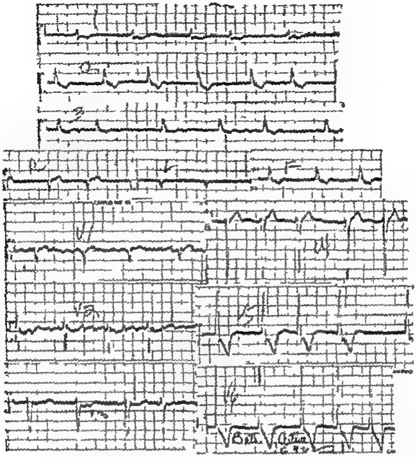

Fig. 2. Electrocardiogram. Rate 62; rhythm, atrial fibrillation; QRS duration 10 seconds. Approximate mean QRS vector (frontal plane) = +75. Approximate mean T vector (frontal plane) = −120. S-T depression with T inversion in Lead I, II, III, aVL, V, V. QS in Lead aVL. Note that R_V exceed R_V.

the center of the most necrotic area of myocardium but usually are irregular dissections which start at the juncture of normal and infarcted myocardium. As Askey[1] emphasizes, it is often difficult to differentiate between septal perforation and rupture of a papillary muscle. The pathophysiologic characteristics of the heart failure and the location and quality of the murmur may be of assistance. If gross incompetence of the mitral valve occurs suddenly, left ventricular failure and severe pulmonary edema will be the preponderant physiologic disturbances. If a large shunt develops between the left and right ventricles, the right ventricle will fail because *it is subjected not only* to an increased volumetric burden but also to a sharp rise in pressure for which it is unprepared. *Large perforations of* the septum tend accordingly to cause marked rises in venous pressure, hepatomegaly, and anasarca. We must remember, however, that the differentiation between left-sided and right-sided heart failure (backward failure of pressure relationships and forward failure of flow — Dickinson Richards) is not always possible. Both of these dynamic disturbances are present when the heart fails and only occasionally is one form clearly preponderant. In the case of our patient the clinical description does not help us to differentiate between left-sided and right-sided *failure*. Physical signs can help to determine whether the lesion is that of septal perforation or rupture of a papillary muscle. The murmur of septal perforation is loudest at the left sternal border from the third *to fifth intercostal spaces. The murmur of*

acute mitral insufficiency associated with rupture of a papillary muscle is loudest at the apex. As we have already read, there were two different descriptions of the location of the murmur. Some examiners stated that the maximal intensity was at the apex. Others specified that it was maximal in the fourth and fifth intercostal spaces along the left sternal border. Thus by the end of the first week of illness we can say that our patient has suffered myocardial infarction and secondary to the myomalacia there has been either a rupture of a papillary muscle (usually the posterior) or a perforation of the interventricular septum. The course of his illness and of the complicating illnesses during the next $4\frac{1}{2}$ years tell us little that we did not know by the end of the first week.

The abrupt onset in the seventh week of pleurisy, cough, fever, and increased congestive failure are consistent with deep venous thrombosis and pulmonary embolization with minor pulmonary infarction. Inasmuch as deep venous thrombosis and pulmonary embolism is the most common complication of congestive heart failure and since he improved promptly with anticoagulant therapy, we need not be disturbed by the absence of signs of inflammation in the legs. Inflammation of the vein is secondary to the thrombosis and clinical evidence of inflammation is more often absent than present.

During this first hospitalization there were signs of both forward and backward failure: the blood and pulse pressures were low and the lungs, liver and cervical veins were congested. The heaving and diffuse apical impulse and the fluoroscopist's impression of a greatly enlarged left ventricle suggest that there was a ventricular aneurysm. If the impulse were described as having different points of maximal force or as being soft on palpation, the impression of an aneurysm would be strengthened. Although the examiners disagreed as to the location of the murmur, they agreed that the murmur was loud and harsh and that a thrill was present. Askey in his review observed that 22 of the 45 systolic murmurs which occurred in 47 instances of interventricular septal defect were accompanied by thrills. Among 37 patients with a ruptured papillary muscle only 17 had systolic murmurs and none had a thrill. If we accept the observation that a thrill was palpable and if we prefer the statement that the murmur was maximal at the border of the sternum rather than at the apex, then we may assume the diagnosis to be that of a septal perforation rather than a rupture of a papillary muscle. The relatively long period of survival favors septal perforation because a number of patients have survived beyond a year and several have survived for 2 to 4 years or longer. The length of survival will depend upon the volume of blood and the pressure which are transmitted to the right ventricle. Rupture of a papillary muscle is distinguished from rupture of chordae tendineae, leads to severe mitral incompetence. Most patients die within hours or days, although 1 patient has lived for 11 months and another for 14 months. Ten years ago one might have been criticized for belaboring an academic point of differential diagnosis. Nowadays precision of diagnosis is of practical therapeutic importance because either of these defects can be approached surgically.

During this first hospitalization the urinalysis showed small amounts of albumin, occasional red and white blood cells, and granular casts and bacteria. This suggests infection of the urinary tract and congestion of arteriosclerotic kidneys. The patient was discharged after 6 weeks on digitalis, diuretics and Dicumarol. He was seen in the outpatient department for the next year and his condition remained constant. The stability of his condition suggests that there was no progressive coronary, myocardial or valvular insufficiency. Furthermore it suggests that his heart had adjusted adequately to its increased burden and that this first hospitalization was precipitated by pulmonary embolization which added a further and intolerable burden to his circulation.

A year after discharge and about $1\frac{1}{2}$ years after his heart attack the patient was rehospitalized because of obstructive jaundice. He tolerated cholecystectomy and choledochotomy, which speaks both for his heart and his doct

condition remained unchanged for another 2 years, and he then re-entered the hospital because of cramping pain in the lower abdomen for the previous month. The physical examination of the heart was essentially unchanged, but the neck veins were distended, the lungs were congested, and there was edema of the legs and over the sacrum. The bowel sounds were hyperactive, and there was generalized abdominal tenderness. No masses were felt, and there was no definite evidence of obstruction by x-ray examination. We are told that the abdominal cramping was unrelated to eating and to bowel movements and that there had been no change in bowel habits. This lack of correlation of the cramps with gastrointestinal function may be simply a faulty history obtained from a sick patient. There is too little information to justify a detailed discussion of these abdominal signs and symptoms. If we attempt to correlate them with the heart disease, we should consider mesenteric vascular occlusion causing an area of adynamic ileus and later ischemic necrosis and peritonitis. I would choose venous mesenteric thrombosis rather than arterial embolization by thrombi formed within the heart because of the prolonged and subacute course. The abdominal signs and symptoms may have been more striking than the protocol suggests, for the patient was operated upon the day of admission despite his edema and pulmonary congestion.

It is to be expected that the congestive failure would increase postoperatively and that it would be difficult to maintain fluid and electrolyte balance. The bloody urine containing fragments suggests severe hemorrhagic cystitis. There may be pyelonephritis, although with necrotizing pyelonephritis one expects increasing degrees of oliguria, fever, and nitrogen retention. We are not told about the urinary output and fever, but late in the illness the blood urea nitrogen was only 35 mg. per 100 c.c.

In summary, we may assume that this patient suffered an acute myocardial infarction on the basis of coronary arteriosclerosis 4 years and 9 months before his death. Seven days after the infarction he developed either perforation of the interventricular septum or rupture of a papillary muscle. I would choose perforation of the interventricular septum because of the relatively long survival and the presence of a thrill. Of the two descriptions of the location of the maximal intensity of the murmur, the parasternal location is more consistent with the thrill and the duration of life than is the apical location. The diffuse precordial impulse suggests a postinfarctional aneurysm of the left ventricle. The terminal signs and symptoms which suggest incomplete obstruction of the bowel and peritonitis may represent venous mesenteric thrombosis. The bloody urine containing particulate material is consistent with infection of the urinary tract.

DR. GREENFIELD: On the first admission an x-ray film of the chest in the anteroposterior and lateral views revealed a moderately enlarged heart shadow. There was some calcification of the aorta. There were increased pulmonary markings, blunting of the right costophrenic angle, and Kerley's "B" lines in the base of the right lung. There was an old fracture of the right seventh rib. Two years and 3 months later there was comparable cardiomegaly and associated vascular prominence. Both costophrenic angles were now blunted. On the last admission, 2 years later, there was no apparent additional enlargement of the heart. There was, however, an accumulation of pleural fluid bilaterally and increased parenchymal markings in the base of the right lung, probably due to compression atelectasis. Two weeks after this film was taken and on the day of death, a portable film showed complete opacification of the left hemithorax, while the right lung appeared to be grossly expanded.

DR. KRAKOWER: The gall bladder removed surgically contained 35 small black stones. The wall was thickened, exhibiting microscopically edema of the mucosa, hypertrophy of the muscular coat, Aschoff-Rokitansky sinuses, and more recent edematous granulation tissue in the adventitia. There were focal areas of lymphocytes and eosinophils in all coats. Three larger stones removed from the common bile duct were yellowish and friable. With patency of the cystic duct but obstruction

of the common bile duct by stone there was increased intraluminal pressure in the gall bladder. The transmural seepage of bile under these conditions may have been favored by the edematous loosening of the wall of the gall bladder which resulted in part from chronic passive congestion on a cardiac basis.

At the laparotomy 3 weeks before death a 14 cm. sector of small bowel with a large infiltrative and ulcerated lesion was removed; the lesion was diagnosed as a lymphosarcoma.

At autopsy, the right pleural cavity contained 1,200 c.c. and the left 1,000 c.c. of clear straw-colored fluid. There were 300 c.c. of similar fluid in the peritoneal cavity and 50 c.c. in the pericardial cavity. Ten discrete large ulcerated infiltrative lymphosarcomatous lesions involved the small intestine. There was also lymphosarcomatous infiltration of the base of the mesentery, forming a matted mass 10.5 by 7.0 cm. Abdominal periaortic, left common and external iliac lymph nodes were also involved. There was, however, no significant lymphosarcomatous involvement of other lymph nodes or viscera. The lungs were heavy and emphysematous with associated areas of compression atelectasis. The right lung weighed 1,020 grams and the left 1,110 grams. Aside from old apical scars, there was at least one pleural and subpleural scar in the right lower lobe which microscopically appeared to represent an old healed infarct. Otherwise there was massive pulmonary edema. The bronchi were filled with thick grayish yellow material. The pulmonary arteries presented thickened walls with disseminated atheromata apparent even in the minor branches. Microscopically, the small radicles of the pulmonary arteries were generally wide and tortuous with evidence of muscular hypertrophy and not uncommonly with fibrous intimal thickenings and infiltration of lipid. The arterioles likewise were commonly thickened both as a result of medial muscular hypertrophy and the deposition of edematous fibrillar tissue. Alveolar capillaries were congested, tortuous, with thrombi in some. There was marked bronchial hyperemia. Hemosiderin-laden histiocytes were common in alveolar spaces. The liver weighed 1,420 grams and was firm and brown. The bile ducts were free of stone. Microscopically, there was portal fibrosis with lymphocytic infiltration as well as irregular circumlobular and intralobular fibrosis. Central and hepatic veins showed variable fibrous mural thickenings. There was not too much sinusoidal congestion. These histologic changes were more in keeping with earlier and repeated bouts of chronic passive congestion than with those expected to follow the release of an obstruction of the common bile duct. The spleen weighed 480 grams. It presented a thickened capsule and was rather soft in consistency. There was some fibrillar thickening of the sinusoidal walls microscopically. There was, however, appreciable lymphoid hyperplasia of follicles and pulp. Few of these cells could be considered to be neoplastic lymphoid elements. Here too, therefore, there was evidence of past chronic passive congestion with superimposed reactive changes presumably resulting from the ulcerative lesions of the small bowel and the infection of the urinary tract described below.

A major contributory factor in the death of this patient was infection of the urinary tract. The bladder was hyperemic with acute ulcers. The prostate, including the median lobe, was enlarged with multiple acute abscesses. The right kidney was reduced to 95 grams and presented the histologic features of an extensive and marked chronic with superimposed acute pyelonephritis. There were acute pyelonephritic changes in the larger left kidney which weighed 140 grams.

The organ of interest was the heart. It weighed 620 grams. Externally, most of its anterior aspect was occupied by the right side as judged by the displacement of the anterior interventricular sulcus to the left. The left heart still formed the apex, however. Posteriorly, there was some displacement of the interventricular sulcus to the right. There was a distinct large aneurysmal bulge to either side of the posterior interventricular sulcus superiorly. There was epicardial thickening over and below the aneurysm. The right atrium was enlarged, measuring 6 cm. from superior to inferior vena cava, and 14.0 cm.

Fig. 3. View of right ventricular [illegible] of the ventricular wall [illegible] and the crescentic slitlike [illegible] defect. A probe passes through the [illegible] indicated by the arrow.

the musculature of the atrium, particularly of the elongated pectinate muscles, and the markedly broadened crista terminalis. The fossa ovalis was enlarged up to 1.9 cm. in diameter. There was no interauricular patency. The opening of the coronary sinus was widened 1.0 by 0.5 cm., with a prominent finely perforated Thebesian valve. There was irregular endocardial thickening about the orifice of the superior vena cava and along the anterior medial wall above the medial portion of the anterior leaflet of the tricuspid valve. There was a distinct bulging of the atrial wall above the medial cusp and the medial portion of the posterior cusp of the tricuspid valve. This bulge was part of the large high posterior and septal aneurysm of the left ventricle. The circumference of the tricuspid valve was increased, measuring 14.5 cm. (normal 12.0 cm.). The cusps were elongated and moderately thickened, with the anterior leaflet measuring as much as 2.5 cm. in length. The right ventricle, and particularly its outflow tract, was enlarged. The inflow tract measured 11.1 cm. in length, the outflow 13.8 cm. In the region of the pulmonary conus the circumference of the tract was as much as 10.5 cm. There was also hypertrophy of the right ventricle up to 0.8 cm. near the base of the inflow tract and 0.7 close to the pulmonary valve. The trabeculae carneae were widened and thickened, as were the elongated (2.2 cm.) papillary muscles, which were 0.9 cm. wide at their base. In continuity with the right atrial portion of the left ventricular aneurysm there was bulging and thinning of the superior posterior portion of the interventricular septum. The endocardium over this was white and opaque. Immediately inferior to this bulge there was an apically inclined crescentic slit 1.4 cm. in diameter, through which a probe could be passed into the posterior inferior portion of the left ventricular aneurysm (Fig. 3). The superior edge of the slit was made up of thinned, readily foldable, fibrosed septal wall which was almost valve-like in character. However, any lateral movement of the latter would have been restrained by the overlying taut chordae tendineae to the medial portion of the posterior leaflet of the tricuspid valve (Fig. 4). The inferior margin of the slit was made up of somewhat thinned

Fig. 4. Enlarged view of the interventricular septal defect seen in Fig. 3 after the restraining trabecular band with its chordal attachment has been reflected with forceps.

septal myocardium with endocardial fibrous thickening. There was endocardial fibrosis of the superior posterior wall of the ventricle for a distance of 2.8 cm. from the base of the tricuspid valve together with a circumferential band of thickening 2.2 cm. wide which involved the papillary muscles. The pulmonary valve measured 8.2 cm. in circumference (normal 8.5 cm.). Its cusps were hemodynamically thickened. The left atrium was likewise enlarged, thin in places but with some muscular hypertrophy up to 0.4 cm. in other places. It measured 5.5 to 7.5 cm. in superoinferior diameter and some 13.0 cm. in circumference. The mitral valve measured 11.4 cm. in circumference (normal 10.0 cm.). Its valves were not very remarkable. The left ventricle was not particularly enlarged although there was hypertrophy. The inflow tract measured 9.2 cm. in length, the outflow tract 12.1 cm. The thickness of the myocardium was 1.7 cm. near the base and 1.2 cm. near the apex. There was a large saccular aneurysm involving essentially the superior third of the posterior septum and the superior medial half of the posterior wall. The orifice to this aneurysm was round and about 5.0 cm. in diameter. This was the measurement after the structures overlying the orifice had been removed and after much of the aneurysm had been protruded through it. Undoubtedly in life the orifice was smaller. It extended from the annulus of the mitral valve to the level of the base of the posterior papillary muscle (Fig. 5). The aneurysm itself measured about 7.0 cm. in maximum superoinferior diameter and 5.2 cm. in depth. The apical portion of the sac was thin and translucent and formed the posterior bulge described externally. Elsewhere the wall varied in thickness up to 0.5 cm. and included a fair amount of well preserved muscle. The interior of the sac had a white opaque appearance with some ridges and a fibrosed stump of a previous structure now not readily recognizable. There were no thrombi. The endocardium, chordae tendineae and somewhat hypertrophied papillary muscles of the left ventricle were otherwise not very remarkable. There was no widening or thickening of the trabeculae carneae. The

Fig. 5. View of left ventricle. The arrows point to the opening of the saccular ventricular aneurysm covered by chordae tendineae and limited above by the annulus of the mitral valve while reaching the level of the papillary muscle below.

circumference of the aortic valve was 8.4 cm. (normal 7.5 cm.). The cusps showed the usual amount of thickening. There was atherosclerosis and calcification at the base of the left aortic sinus and valve and the posterior half of the right. The coronary orifices were wide. There was, however, an area of narrowing of the right coronary artery 2.0 cm. from its orifice. Beyond that the artery in its distal 3.5 cm. was small and thick with partially patent or obliterated lumen. The posterior descending coronary was formed by the right. It was small, thin walled and patent. The left descending coronary artery had an ample internal circumference, maximally 0.9 cm., with little atherosclerosis. The left circumflex had an initial circumference of 0.7 cm., then narrowed to 0.4 cm. and could not be traced in the posterior sulcus beyond its lateral obtuse branch. It too was patent with little atherosclerosis. However, the arch, thoracic and abdominal portions of the aorta were appreciably involved, particularly the latter. Even here there were few plaques that were calcified or ulcerated. The pulmonary artery 2.0 cm. above the valve measured 8.3 cm. in circumference and less than 1 mm. in thickness. These figures are a little above the usual range. The circumference of the aorta at a comparable level was 7.1 cm. and its wall was 2.0

mm. in thickness, values within the normal range.

It is clear that this man developed thrombosis of a dominant right coronary artery and with it an in part transmural, in part subendocardial necrosis of the superior posterior interventricular septum and the superior portion of the posterior wall of the left ventricle. Following this there was perforation into, and communication with, the right ventricle. In the course of and after repair of the infarct, this area became a large saccular aneurysm. Despite these complications and with the aid of digitalis, cardiac function was fairly well maintained. In keeping with this were the findings of relatively mild chronic passive congestion of the abdominal viscera. In the absence of cardiac catheterization there is no way of estimating how much of a left-to-right shunt there was or the level of the average right intraventricular systolic pressure. It can only be assumed from the size and thickness of the outflow tract of the right ventricle, that of the pulmonary artery, and the sclerotic changes in the pulmonary arterial radicles that both volume output and pressure were increased. It gives us no clue as to the extent of the increase, however. For example, the average right ventricular systolic pressure ranged from 25 to 88 mm. Hg in 6 cases with somewhat similar postinfarctive complications reported in the literature.[3]

Doubtless, in terms of survival, the extent of the left-to-right shunt and the degree of increase in right ventricular pressures are of importance.

It is of interest that in a review of the postmortem cardiac findings reported in cases of prolonged survival after infarction of the left ventricle with interventricular septal rupture, two features appear to be constant. One is the presence of a good-sized myocardial aneurysm. The second is most commonly a tract which leads obliquely from the aneurysm to the right ventricle. It is reasonable to assume that the character of blood flow within and the emission pressure from a noncontractile or poorly contractile aneurysmal sac would be different from that in the left ventricle proper. The combination of such an aneurysm with an indirect tract rather than a direct perforation would therefore favor reduced flow of blood into the right ventricle under reduced pressure. These reductions in flow and pressure were all the more favored in the present case by (1) the real saccular character of the aneurysm with a relatively narrow orifice and not merely a bulge of the ventricular wall, and (2) the valve-like superior lip of the crescentic opening of the tract, which could have effectively closed the opening during diastolic stretch while being held in partial check by the overlying chordae tendineae during the systolic phase. The excellent state of the left coronary arteries which enabled the hypertrophied myocardium, both right and left, to obtain an adequate amount of blood undoubtedly played an important role, too, in the prolonged survival of this patient.

Diagnosis. Postmyocardial infarction of superior posterior interventricular septum and posterior wall of left ventricle with saccular aneurysm and septal rupture. Survival of 4 years and 9 months. Old occlusion of dominant right coronary artery. Lymphosarcoma of small intestine with mesenteric and abdominal lymph node metastases. Chronic and acute pyelonephritis, right; acute pyelonephritis, left, with acute ulcerative cystitis and prostatic abscesses.

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Fundamentals of clinical cardiology

Re-evaluation of therapy of acute myocardial infarction

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The rate of mortality from acute myocardial infarction has not declined commensurately with the general advancement of medical technology. Anticoagulant therapy, which has decreased the incidence of thromboembolic complications only slightly and the mortality rate even less, has perhaps distracted the clinician from the search for more successful therapeutic approaches. In a discussion in 1953 of deaths from acute coronary failure (sudden unexpected death in the absence of myocardial rupture, pulmonary embolism, or acute congestive failure), Achor speculated that deaths from this cause might be the subject of more intensive study and a rewarding place to reduce the incidence of unexpected death among patients with coronary heart disease.[1] These considerations have prompted this review of the present concepts in the treatment of acute myocardial infarction. Special attention will be directed to the role of anticoagulant therapy, to the development of intensive care units which utilize newly devised electronic aids for monitoring, for restoring normal cardiac rhythm, and for resuscitating the heart, and to the present status of fibrinolytic agents in the therapy of acute myocardial infarction.

General measures

Certain principles of therapy in acute myocardial infarction appear to be well accepted and do not warrant discussion herein. These include (1) the administration of oxygen and adequate analgesia while pain persists, (2) prompt treatment of associated hypotension or congestive heart failure, (3) physical rest for the heart (although rest in bed is traditional in the treatment of myocardial infarction, increased comfort and lowered cardiac output are afforded the patient when he is allowed to rest in a chair a portion of each day beginning early in the postinfarction period, and this should be encouraged), and (4) conscientious attention to the details of good general care, such as proper sedation, avoidance of constipation, periodic deep breathing, and mild exercise of the muscles of the legs. Tillman, emphasizing intensive professional care by the nurse and physician and excluding the use of anticoagulants, noted a mortality rate after the first 24 hours of 11 per cent for patients with acute myocardial infarction. This rate is lower than that usually reported for acute myocardial infarction from studies that employed anticoagulant therapy.

Anticoagulant therapy

Anticoagulant therapy after acute myocardial infarction is used to prevent complications of intravascular or intracardiac thrombosis and of embolism, both of which may be enhanced by ischemic injury

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of the endocardium and by subsequent prolonged physical inactivity. A decreased incidence of clinically recognized thromboembolic events and a lower incidence of mural thrombosis at necropsy have been reported among patients so treated.[3] Criticism of routine anticoagulant therapy has been based on the difficulties inherent in such treatment, the significant incidence of hemorrhage, and the relatively low incidence of thromboembolic complications when anticoagulant drugs are not used. In addition, there is still some doubt that the routine use of these drugs significantly reduces mortality from acute myocardial infarction. The widespread use of anticoagulant drugs has complicated the problem of studying their effectiveness in the clinical setting, however, for the physician now wonders whether he can ethically withhold such therapy for the purpose of conducting a controlled study. In an attempt to evaluate the need for further prospective study of the effect of anticoagulant therapy in acute myocardial infarction and to determine whether the withholding of this therapy in patients selected for a control group would be reasonable, we have reviewed some of the recent experience in the treatment of acute myocardial infarction at the Mayo Clinic. This review was an uncontrolled retrospective study undertaken to determine the feasibility of a subsequently controlled prospective clinical study.

The case records of all residents of Rochester, Minnesota, who were registered at the Mayo Clinic for acute myocardial infarction during the years 1945 through 1959 were reviewed. In the group studied were 295 patients who had a total of 355 such infarctions. Patients treated at home as well as those treated in the hospital were included in this study. Several anticoagulant drugs were used during these years. Bishydroxycoumarin (Dicumarol) was the oral agent used most often; initial anticoagulation was achieved with heparin in a few cases and with ethyl biscoumacetate (Tromexan) in others. The status of anticoagulation was evaluated by frequent (usually daily) determinations of the prothrombin time. Patients who died during the first 24 hours after their acute attack were excluded because the role of the anticoagulants could not be evaluated during this time.

Thromboembolic complications were recognized clinically in association with 3.3 per cent of the 239 infarctions treated with anticoagulants and in 5.1 per cent of 116 not treated with anticoagulants (Table I). The only fatality from thromboembolism was due to embolic occlusion of a femoral artery in one case in which anticoagulants were not used. During the first 6 weeks of convalescence from an acute myocardial infarction, there was clinical evidence of reinfarction in 11 instances. When these 11 were added to the 14 peripheral thromboembolic accidents, the total thromboembolic rate increased to 5.8 per cent of infarctions treated by anticoagulants and 9.4 per cent of those not treated by anticoagulants. Hemorrhagic complications occurred during the hospitalization period in 3.8 per cent of the infarctions treated by anticoagulant drugs (Table II). No fatalities resulted from hemorrhage. Verified myocardial rupture occurred 24 hours or more after 1.7 per cent of the infarctions treated by anticoagulants and after 4.3 per cent of those not so treated. Death during the first 6 weeks resulted from 17.6 per cent of the 239 infarctions treated by anticoagulants and from 19.8 per cent of the 116 not so treated. Factors in the selection of infarctions in which anticoagulant therapy was given are not evaluated in this review. The data show that only minor reduction of thromboembolism and improvement in mortality rate could be attributed to anticoagulant therapy and suggest a need for additional prospective studies of the use of anticoagulants in acute myocardial infarction. The ethical propriety of withholding this therapy in patients designated to comprise a control group would seem to be a corollary to this conclusion. At this time, anticoagulant therapy appears to be successful in decreasing the thromboembolic phenomena related to the venous system, but its effectiveness in preventing arterial thrombosis and embolization remains doubtful.[6,7] For this reason, controlled studies on the prevention of arterial thromboembolic disease by short-term and long-term anticoagulant therapy should be encouraged.

Table I Incidence of clinically recognized thromboembolic complications of 355 acute myocardial infarctions

Type or location	Anticoagulants: Used (239 infarctions) Number		Used Per cent	Not used (116 infarctions) Number		Not used Per cent
Venous thromboembolic complication	7		2.9	4		3.4
Iliofemoral thrombophlebitis		1			1	
Pulmonary embolus		5			3	
Multiple pulmonary emboli		1			0	
Arterial thromboembolic complication	1		0.4	2		1.7
Cerebral vascular accident		1			1	
Femoral artery occlusion (fatal)		0			1	
Subtotal	8		3.3	6		5.1
Recurrence of coronary artery thrombosis or myocardial infarction during first 8 weeks after acute myocardial infarction	6		2.5	5		4.3
Total thromboembolic complications	14		5.8	11		9.4

Table II Incidence of hemorrhagic complications of 239 acute myocardial infarctions treated with anticoagulants

Complication	Number		Per cent	Prothrombin time (Quick) seconds
Major	4		1.7	
Massive epistaxis		1		47
Gastrointestinal hemorrhage		1		33
Hemarthrosis		2		25 and 40
Minor	5		2.1	
Hematuria		2		101 and 73
Hemoptysis		1		104
Conjunctival hemorrhage		1		37
Multiple hematomas		1		Unknown
Total	9		3.8	

Intensive care unit

We believe that a significant decrease in deaths from acute myocardial infarction will result from the prevention of many deaths presently ascribed to "acute coronary failure" (sudden death in the absence of reinfarction, myocardial rupture, congestive failure, or thromboembolism). Necropsy studies during the years 1947 through 1952 revealed that coronary heart disease accounted for 32 per cent of the deaths in adults (necropsies were performed in 66 per cent of all deaths) among residents of Rochester, Minnesota.[8] Of the deaths due to coronary heart disease 43 per cent were attributed to acute coronary failure. The mechanism in most instances of sudden death is assumed to be the development of ventricular fibrillation or other arrhythmia incompatible with adequate support of circulation. Today these complications are potentially reversible provided that there is prompt recognition followed by immediate intensive care. Closed-chest cardiac massage as described by Kouwenhoven and associates[9] can be initiated by properly trained personnel to maintain life in the event of ventricular

fibrillation or standstill until help can be obtained and either defibrillation or application of a cardiac pacemaker or both can be carried out. The recent introduction by Lown and associates[10] of a new electronic device using the principle of synchronized capacitor discharge offers promise of successful and prompt termination of ectopic rhythms. Kecvil and co-workers[11] have demonstrated that these techniques can be successful in the small community hospital even without an in-residence house staff.

Among the 295 patients with 355 acute myocardial infarctions considered in the present study, 58 (20 per cent) who either died of acute coronary failure after acute myocardial infarction or whose hospital course was complicated by cardiac arrhythmia such as complete heart block possibly could have benefitted from a constant care unit. In addition, many of the deaths that occurred during the first 24 hours after the myocardial infarction were due to acute coronary failure. If only one fourth of these deaths could be prevented through the application of an intensive-care unit, the reduction in the mortality rate possibly would far exceed any reduction achieved by anticoagulation therapy.

Thus, the ideal therapy for acute myocardial infarction must include constant nursing supervision plus the use of electronic instruments necessary for the detection and management of acute coronary failure.[3] We envisage the development of an intensive-care ward similar in principle to the postcardiac surgery ward to meet these needs. Depending on the size of the hospital, such a unit might consist of 2 or 20 beds, preferably subdivided into individual units to assure privacy and quietness. The round or rectangular shaped ward with individual peripheral rooms and a central nursing station from which all patients can be viewed at a glance might be the ideal design. The intensive-care ward would be staffed by specially trained nurses and physicians who are intimately familiar with each step of resuscitation and external cardiac massage and with the cardiac monitor, pacemaker, and defibrillator. Ideally, there should be continuous electrocardiographic monitoring of the cardiac rhythm and monitoring of vital signs for as long as 2 weeks after acute myocardial infarction. Recent advancements in electronic telemetry make possible the monitoring of several physiologic parameters simultaneously with apparatus which is not cumbersome to the patient and which does not limit his motion and ambulation. Additional controlled studies need to be made in order to evaluate this type of therapeutic approach.

Thrombolytic therapy

The clinician's problem with regard to thrombolytic therapy in acute myocardial infarction is to administer the necessary amount of a satisfactory clot-lysing agent to the patient whose coronary artery has been occluded by a thrombus within the previous several hours, to accomplish this administration without substantial discomfort or risk to the patient, to monitor the thrombolytic effect during administration, and finally, to accurately assess the results of this treatment. These challenges have stimulated many interesting investigations in the past few years, some of which have indicated that thrombolytic agents are a helpful therapeutic adjunct for acute myocardial infarction and other thromboembolic diseases and have brought the related problems into sharper focus.

At present, the most satisfactory agent available is a combination of fibrinolysin and the more important component, the activator, streptokinase (Thrombolysin). Although Thrombolysin is at present being investigated in animals and man with success, it has some disadvantages. It contains pyrogens or other impurities that cause significant side effects, and it is antigenic, which makes advisable the carrying out of a dose prediction test such as that of Johnson and Sherry,[12] in order to determine the dose of streptokinase which will be large enough to overcome the neutralizing antibodies and still be large enough to lyse the clot. The antigenic property also makes repeated administration risky because of allergic reactions.

Time is important to the success of clot lysis. In studies on animals, the best results are obtained when clot formation has been going on less than 10 hours

It is impossible to utilize thrombolytic therapy this rapidly in some patients with acute myocardial infarction. The thrombolytic agent can be administered intravenously or intra-arterially. The former method requires 6 to 8 hours of administration of the properly estimated dose with close monitoring of coagulation and clot lysing factors. Boucek and Murphy[14] have demonstrated that Thrombolysin can be safely and effectively administered by brachial artery–aorta catheter; the agent is automatically injected into the root of the aorta electronically by every fourth R wave of the electrocardiogram. Not enough evidence exists to say with surety whether intra-arterial or intravenous fibrinolytic administration might prove the more efficacious and practical technique in lysis of clots in the coronary artery.

A further problem is the uncertainty of the presence of an acute coronary thrombus in the patient with acute myocardial infarction. Somewhere between 40 and 80 per cent of acute myocardial infarctions probably are caused by a thrombus. The remainder of the infarctions may be caused by atherosclerotic plaques, coronary arterial emboli, or hemorrhage into a plaque.

Evaluating the results of therapy with thrombolytic agents, a situation like that after using anticoagulants, is most difficult. Ruegsegger and associates[1] in a widely quoted study that employed Thrombolysin after induction of clots in the coronary arteries of dogs have offered some hope that thrombolytic therapy may be of value in the treatment of acute myocardial infarction. They demonstrated salvage of ischemic (non-necrotic) myocardium even prior to lysis of the major obstructing clot, due to lysis of micro-thrombi with restoration of collateral circulation and cellular nutrition. In 7 of the control animals the clots retracted slightly within 12 to 15 hours and in 1 the clot dissolved rapidly (spontaneous fibrinolysis). The coronary thrombi in 8 treated animals were lysed in 3 to 4 hours. Results in human beings have been evaluated on the basis of changes in pain, electrocardiogram, and transaminase values and occasionally on the basis of necropsy findings. The absence of a thrombus at necropsy is impossible to evaluate if there is no proof that a thrombus existed originally as the cause of the infarction. Changes in pain, electrocardiogram, and transaminase values in the course of acute myocardial infarction are variable enough to make the interpretation of differences between treated and untreated conditions exceedingly difficult.

Monitoring the effect of Thrombolysin is also a problem. At least 10 different methods have been employed, but none that gives completely satisfactory results is easy to use. A detailed description of these methods can be found in the recent literature on fibrinolytic agents.[16] Epsilon aminocaproic acid is now available as a possible antidote for the hyperplasminemic state which can result in a bleeding diathesis.

Thrombolytic therapy for acute myocardial infarction is new but may prove to be of help in decreasing the mortality and thromboembolic complications of acute myocardial infarction. In an excellent summary of the status of fibrinolytic therapy, Sherry[17] stated that the development of this therapeutic method is a combined biochemical and clinical problem which needs further scientific advancement before clinical trials can be encouraged except under circumstances of strictly controlled clinical investigation. Preliminary observations are encouraging, but results cannot be scientifically evaluated as yet.

Summary

A review of results of therapy for acute myocardial infarction was undertaken because the decline in the rate of mortality from this disease has not been commensurate with the general advancement of medical technology. Conscientious general care and early chair rest are emphasized. A retrospective study of the use of anticoagulants revealed a slightly decreased incidence of thromboembolism and of mortality in the cases in which anticoagulants were used. Although anticoagulant drugs are probably of some benefit, their use should not detract from the search for better methods of salvaging life after myocardial infarction. Intensive-care units

therapeutic devices and medical personnel trained and drilled in the procedures for cardiac resuscitation are considered to be an urgent need. Intensive care units are likely to be the best means now available to clinicians for decreasing the rate of mortality from acute myocardial infarction. The use of thrombolytic agents now quite new may become a widely employed and useful means of helping the patient who has acute myocardial infarction. At present the need in this area is for further clarification of the biochemical effects of thrombolytic agents, the development of more practical means of administration and control of the agents, the search for improved agents, and the evaluation of thrombolytic agents in animals and in the various thromboembolic diseases of man under careful investigational conditions.

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Appraisal and reappraisal of cardiac therapy

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Treatment of paroxysmal supraventricular tachycardia in infancy

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Paroxysmal supraventricular tachycardia of infancy occurs most prominently in the first month of life, with a decreasing frequency over the next 3 months. Ventricular conduction is usually 1:1; the rate varies from 160 to 300, with 180 to 200 usually the critical level.

Brief episodes which last a few hours cause no clinical difficulty and are not a problem in treatment. Longer episodes (48 hours or more) almost invariably produce congestive heart failure even though there is usually no underlying heart disease, and are an urgent indication for treatment. Whether the focus is clearly in the atrium, or in the node, or impossible to define, the therapy is the same and somewhat different from that of paroxysmal atrial tachycardia in the adult.

Treatment. Obviously all modalities of nursing care and adjunctive therapy will be directed toward such a sick infant, i.e., appropriate antibiotics if infection is present, humidified oxygen, proper positioning, a minimum of handling, feeding by nasogastric tube or parenteral fluids, and morphine for the restlessness and irritability. In some the paroxysms terminate spontaneously, but this cannot be predicted for the individual patient. Reflex vagal stimulation by carotid sinus or eyeball pressure or by induced vomiting is rarely effective. Specific cardiac therapy is directed toward suppression of the ectopic focus of impulse formation.

Digitalis is almost invariably effective in idiopathic supraventricular tachycardia and slightly less so in these arrhythmias associated with the Wolff-Parkinson-White syndrome (10 per cent of the cases). Digoxin, because of rapid absorption, relatively rapid dissipation, and uniformity of action whether given intravenously, intramuscularly, or orally, is the glycoside of choice. The digitalizing dose in the first year of life is 75 μg per kilogram of body weight, except in premature infants, in whom 50 μg is probably safer. Half the calculated dose, either orally or intramuscularly, depending on the condition of the infant, is given initially, and then half of the remainder is given in 4 to 6 hours and the balance 6 to 8 hours later.

Thus presumably full digitalization will have been achieved within a period of 12 to 14 hours. If by then the arrhythmia has not been converted to a normal sinus mechanism, an additional one fifth of the digitalizing dose can be given at subsequent 4 hour intervals until conversion is achieved or toxicity precludes further administration. Frequent electrocardiographic monitoring is mandatory for recognition of either conversion or evidence of toxicity. If conversion is accomplished, a

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daily maintenance dose of digoxin is continued as one third to one fifth of the digitalizing dose, started 8 to 12 hours later and given in two portions.

Usually, digitalis is so successful in the conversion of paroxysmal supraventricular tachycardia to normal sinus rhythm in infants that, even in large pediatric centers, other drugs are rarely necessary. Should digitalis fail, quinidine is the next drug to be used. Full digitalization is preferred prior to its use. Quinidine can be administered safely in doses of 4 to 6 mg. per kilogram of body weight by nasogastric tube at 2 hour intervals for four to five doses. Here, too, frequent electrocardiographic monitoring is necessary for recognition of toxic manifestations, these being, as with digitalis, premature ventricular contractions and widening of the QRS interval.

Almost all attacks of paroxysmal supraventricular tachycardia will be terminated by the use of digitalis alone or with quinidine. A few persist, however, and not uncommonly so much time has then elapsed that the clinical condition has become extremely critical. Therefore, despite the risk involved, the use of the rapid-acting cholinergic or cholinomimetic drugs, such as neostigmine or methacholine, in a single dose becomes imperative. Neostigmine may be given subcutaneously in a dosage of 0.013 mg. per kilogram of body weight. The recommended dosage of methacholine is 0.045 to 0.048 mg. per kilogram of body weight given subcutaneously, but in our experience a dosage of 0.50 mg. per kilogram of body weight has been effective. Constant electrocardiographic monitoring must be maintained subsequent to the administration of these drugs. It should be emphasized that methacholine be administered only by subcutaneous route and that atropine be readily available to counteract the side effects. In addition to the varying degree of heart block or cardiac arrest, vomiting, lacrimation, salivation, and sweating may be prominent manifestations of less serious nature. Severe bronchospasm may be precipitated; this may even require the administration of epinephrine in addition to atropine intravenously. The fivefold potentiating effect of neostigmine on the cardiac action of methacholine should also be noted. Deaths have been reported with this condition. Intravenous atropine may abolish the reaction and must be used promptly. There is no significant experience with the use of procaine amide or with vasopressors such as phenylephrine or norepinephrine in the supraventricular tachycardia of infancy. To our knowledge, electrical countershock has not been used in infants, but in view of its known effectiveness for such arrhythmias in adults, there seems to be no reason why it could not be used.

Prophylaxis. After successful termination of the attack of paroxysmal supraventricular tachycardia, the question of the possibility of future attacks arises. It is comforting to know that in infants with the "idiopathic" variety whose initial attack has occurred within the first 4 months of life, recurrences are unlikely after a year. In those whose attacks are associated with the Wolff-Parkinson-White syndrome, recurrences are rare after about 18 months of age.

Although it is usual for an infant to have but one attack, this is not predictable for the individual. Consequently, it is advisable that the infant whose attack has responded to digitalis be kept on a maintenance dose for the next month. With a recurrence, redigitalization is indicated until 1 year of age or so in the "idiopathic" group and until 18 months of age in those with the Wolff-Parkinson-White syndrome. In the latter patients, as in initial therapy, in addition to digitalis, quinidine may also have to be administered in doses of at least 6 mg. per kilogram of body weight four times a day and often in considerably larger amounts. Here, too, medication may be stopped after 1 month and observation for recurrence instituted. In those who require neostigmine or methacholine for conversion, prophylaxis with these drugs cannot be maintained. Should there be recurrences in such patients, it is advisable to initiate therapy with digitalis, to be followed by quinidine if necessary, before resorting to the parasympathomimetic drug.

Annotations

Trial by digitalis

By observation and conversation with medical students and house officers we have been dismayed to find that 178 years after Withering's account an appalling set of beliefs about digitalis is at large. Erroneous doctrines concerning digitalis seem to have two principal origins (a) slipshod practices that have evolved through default in the large volume clinics of charitable institutions despite university ties and (b) the medical literature. False assumptions and ready recipes constitute the major impediment to learning from observation. Since such presuppositions unfortunately lead to courses of action we have prepared a list of common offenders and suggested antidotes.

1 There is a practical average digitalizing dose and a practical average maintenance dose of digitalis—either total or weight corrected. The modifier *practical* indicates that this dictum contains lip service but not adherence to the principle of expecting a wide spectrum of individual variation in biologic phenomena. Gold[1] as did Withering[2] advocated an appreciation of the importance of individual variation in the therapeutic bioassay of digitalis. Unfortunately Gold's use of the term average full digitalizing dose[3] in a statistical and pharmacologic sense has severely damaged his advocacy and left a residual yearning for a uniform dose. *There are several ways in which the administering observer can get away with using a uniform dose and not appreciate the inappropriateness of his behavior.* (a) He can choose a uniform dosage small enough to avoid poisoning more than a very low percentage of his population sample (b) He can ignore the beneficial effect of bed rest and attribute improvement to digitalis therapy alone (c) He can then further mask the inadequacy of the underdigitalizing regimen by supplementing it with the frequent administration of diuretic agents (d) He can delegate the responsibility for making the appropriate observations and corrections in dosage to the nurse or patient by standing orders or standing instruction. But the careful observer without these clinical blind spots must conclude that digitalization is a human bioassay and human bioassay *must* be carried out under the watchful *scrutiny* of a physician.

2 Transfer between digitalization with a fast acting digitalis preparation and maintenance with a slow acting preparation is easy. The methods are dichotomous either (a) shift to a maintenance dose and allow for no rapid excretion[4] or (b) assume total immediate excretion and redigitalize completely. The immediate shift to maintenance dose after digitalization with a fast acting preparation involves a special application of the fallacy described in the preceding paragraph. In this instance the fact is ignored that rest and immediate digitalization for congestive heart failure can be followed by long periods of symptomatic improvement (and further extended by diuretic therapy) *without* any digitalis maintenance. Only under the circumstances of long term observation and critical control of the other factors could the response of weight to workload be expected to differentiate between those with adequate maintenance dosage and those without.

If there is the wide variation in human response that we believe exists, immediate redigitalization with a slow acting preparation could be and certainly is sometimes uneventful. However the careful observer employs frequent electrocardiographic monitoring during the analogous period of cautious slow redigitalization with leaf and often alters the dosage because of finding such early toxic manifestations as extrasystoles or delayed AV conduction. Therefore he has reason to suspect that with less careful monitoring minor toxicities are overlooked and sudden disasters which are indeed digitalis related go unexplained only because of insufficient evidence.

3 There is no harm from prophylactic digitalization prior to operation and possibly some good.[5] ("Digitalis cannot harm the healthy heart.") This belief appears to stem from a false analogy between prophylaxis and therapy, although it is well known that digitalis will produce premature beats and more serious disturbances of rhythm; it is also well known that sometimes the administration of digitalis by improving cardiac output and increasing coronary blood flow can abolish ischemic extrasystolic foci. Because the antiarrhythmic effect of digitalis can on more critical clinical evaluation be shown to be rational therapy of mild congestive heart failure and its sequel we should avoid confusing necessary preoperative treatment and stabilization with unnecessary prophylaxis. Cursory examination should not be cloaked by the use of a powerful drug on the supposition that there may be undetected myocardial weakness. There are two serious oversights in such a justification to prophylactic digitalization. The first is [illegible] turn to the fallacy that an appropriate [illegible] can be arrived at without individual t[illegible] st[illegible] symptom [illegible] in asympt[illegible] titrat[illegible] Th[illegible]

econd fails to consider the hazard to the patient if a preoperative or postoperative electrolyte imbalance depletes the patient's myocardium of potassium and sensitizes it to the toxic effects of digitalis

4 Some digitalis preparations have a wider therapeutic margin than do others[2,4] After the initial enthusiasms abate the new preparations *have been found to have the same toxic manifestations* and same narrow therapeutic margins as the old

5 Rapidly inactivated digitalis preparations are safer to use in patients who are in precarious condition and likely to be intoxicated Despite widespread realization that the therapeutic margin is narrow there is still advocacy of daily doses of the same magnitude as that margin Assume that a slow preparation (as digitalis leaf or digitoxin) requires 3 weeks for inactivation in a given patient and in that same patient a fast preparation (as digoxin) requires only 5 days In a comparison of *these two effective downslopes of loss of digitalis* effect several conclusions are reasonable (a) A *proportionately larger dose of the fast preparation* will be required each day to maintain digitalization (b) Because a loss of 10 per cent of the digitalizing dosage may result in a loss of far more than 10 per cent of the actual digitalizing effect the necessity *for a replacement or maintenance dosage with the* fast preparation of greater than 10 per cent of *the digitalizing dosage implies a very great loss of* digitalizing effect between doses ( ) On the other hand a maintenance dosage in the range of 25 per cent of the digitalizing dose implies increasing likelihood of intoxication after each dose (d) Thus the events of intoxication or loss of digitalizing effect are more likely with adequate daily dosages of the fast drug if any degree of the variability which is characteristic of living systems is encoun*tered The up-swing into toxicity can be minimized* by reducing the time interval between doses of the fast drug thus cutting the required dosage There is little to be gained from this feat however because under conditions of *comparable vigilance* the duration of toxic effect has been shown to be the *same* for both fast and slow preparations [5]

6 The differential diagnosis between underdigitalization and overdigitalization is easily and safely *resolved* by a test with a fast acting fast excreted digitalis glycoside or calcium The mor*tality rate of 5 per cent with the original acetyl* strophanthidin test in the hands of experienced clinician-electrocardiographers[1] should be sufficient warning to proscribe its clinical application However in a similar small series after careful limitation of the dosage and the rate of administration no fatality occurred[7] Calcium ion has a toxic effect similar to that of digitalis but its usefulness in assay is not clearly established although the hazard certainly is[1,2]

7 Either nausea anorexia or headache is usually the first sign of digitalis poisoning Disturbances in rhythm especially the appearance or increase in frequency of ventricular premature beats usually precede one of the common symptoms The need for systematic electrocardiographic observation during digitalization is obvious

8 Potassium ion is the specific antidote for digitalis poisoning Lown and Levine[20] have called attention to the distinction between digitalis poisoning by an actual excess of digitalis and sensitization of the myocardium to digitalis by potassium deficiency Since the symptoms and serious disturbances of rhythm are identical and the serum potassium may be normal in the presence of a total *bodily deficit of potassium the historical docu*mentation of loss of potassium (commonly by diu*retics or vomiting) is essential to the distinction* Its practical importance lies in the danger of compounding digitalis poisoning by excess with potassium in excess thus increasing the hazard of heart block[21]

We are tempted to thank fortune that the more common evils tend to demonstrate error on the side of homeopathy rather than poisoning However this may be winnowing by natural selection because the immediate sequels of undertreatment are less spectacular than those of overtreatment House *officer dynasties in the outpatient clinics continue* to foster the tradition of one tablet per 10 pounds of body weight and one tablet a day thereafter Fortunately poisoning during digitalization is frequently avoided by emesis common sense or occasionally the physician's warnings and the phase of homeopathic maintenance is made hazardous only because continuing or recurrent signs of failure call forth heroic iatrogenic diuresis and *electrolyte imbalance rather than adjustment of* the dosage of digitalis

How is the young physician to avoid becoming ensnared by these and other foolish notions yet to be propounded? We would emphasize reliance not on authority but on careful observation critically examined with a scientific attitude of mind Our advice may be summarized in the following points

1 Read Withering's An Account of the Foxglove[3] Mackenzie's Chapter XXX on auricular fibrillation in *Diseases of the Heart* 3rd edition[23] and Kay's Clinical Use of Digitalis Preparations[24] Each should be appreciated in its historical context For example Withering's classification of dropsies likely to respond to digitalis we now know to be faulty and in recent times the treatment of rhythm disturbances has greatly improved since Kay's review[2,25]

2 *Realize* that there is now opportunity to know more than Withering knew about the ways in which digitalis can kill *Therefore resolve to do no worse* and possibly better than he did by observing for electrocardiographic evidences of toxicity—especially the development of ventricular premature beats or an increase in their frequency

3 Remember that in seeking the proper amount of drug to relieve the dropsy today's physician has in addition Sir James Mackenzie's observations on the action of digitalis in atrial fibrillation[23] *Therefore* seek two therapeutic end points (a) slowing of the ventricular rate in the presence of atrial fibrillation and (b) relief of symptoms and maintenance of near-dry weight in the treatment of congestive heart failure Be critical however of your own efforts and in the first instance use the electrocardiograph to be certain that either speeding or slowing of the heartbeat does not herald the toxic

development of heart block or an independent lower rhythm. In the second instance do not underestimate the contribution of bed rest and do not deliberately mask your own observation with unnecessary diuretic agents.

4. You are now armed. Do not acquire extra baggage from the doctrinaires. If you remain both vigilant and skeptical, you can continue to learn from observation from *each* human being on whom you are called to assay digitalis.

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Population study of arterial pressure

Several attempts have been made to add to knowledge of essential hypertension by the study of blood pressure in the general population. It has been shown that arterial pressure is continuously distributed and that in unselected individuals for whom clinical or other evidence of associated abnormality is lacking only an arbitrary division can be made between normotensive and hypertensive.[1,2] From this evidence it was concluded that essential hypertension is not a disease entity, that the genetic influence on

pressure is multifactorial and that environmental influences on pressure must be important.[4] Objections were taken to this interpretation on the ground that it was not in accord with clinical experience and that bimodality could be demonstrated in distribution of pressures of selected groups—for example, sibs of hypertensive propositi.[4] It was suggested, therefore, that essential hypertension is a disease entity perhaps attributable to a single dominant gene.

A possible reconciliation between these viewpoints was proposed in the light of evidence concerning the distribution of arterial pressure in a large industrial population.[6] Here too it was shown that pressure is continuously distributed in unselected males, and reported irregularities of distribution interpreted as bimodality were considered to be due to small numbers. It was suggested that differences of opinion about the nature of essential hypertension arise chiefly from the fact that, defined as elevation of blood pressure without apparent cause, it must include two different groups of cases: those in which no pathologic condition is present and which can probably be regarded as the upper end of the distribution in the general population, and those in which associated pathologic conditions are present but unrecognized. The proportion of the latter in a series from which recognized secondary cases have been removed is probably much greater at very high than at moderately high levels of pressure. It was proposed that patients with raised arterial pressure could usefully be divided into two groups: pathologic types, in which associated anomalies are present (whether recognized or unrecognized), and physiologic types, in which no pathologic condition is present and which can properly be regarded as being at the upper end of the distribution of pressure in the general population.

This distinction throws no light on the significance of high blood pressure (both in respect of subsequent trend of pressure and clinical prognosis) in the absence of associated anomalies (i.e., in the physiologic type). Clearly it will be desirable to follow the trend of pressure by continuous observation of the same individuals over a considerable period of time, but some of the difficulties of doing so have been underlined by a recent report based on two British populations. Arterial pressures of 833 Birmingham men were measured by eleven general practitioners on two occasions separated by an interval of 3 years. No special precautions were taken and mean differences between readings were: systolic, 17.4 mm.; diastolic, 10.0 mm. Hg. Coefficients of correlation between first and second readings were: systolic, 0.63; diastolic, 0.50. Similar observations were made on 300 men in two surveys in the Rhondda Fach and Vale of Glamorgan after intervals of 4 and 4½ years, respectively. All pressures were measured by one observer who took certain precautions, but their effect on consistency of readings was not great. Mean changes in systolic and diastolic pressures were 14.6 and 8.4 mm. Hg, and coefficients of correlation were 0.72 and 0.63, respectively. Not surprisingly, first readings which were low tended to be higher at the second reading, whereas those which were high tended to fall, but the amount of scatter about the mean did not change appreciably.

Those discrepancies between consecutive measurements of blood pressure on the same individuals show the unreliability of the diagnosis of hypertension which rests on a single record of casual pressure. For example, in Birmingham the proportions of men with systolic pressures over 180 mm. Hg was approximately the same at both surveys. But of 216 men with systolic pressures above this level at the first examination, 85 had pressure below it at the second. Of 617 men with pressures under 180 mm. Hg when first examined, 77 had pressure above that level at the later examination. Similar changes were observed in both Birmingham and South Wales data using other criteria of hypertension.

An anomalous feature of the Birmingham findings was that, although data from each survey showed the expected increase in systolic pressure with advancing age, mean pressure was no higher at the second examination than at the first, although the men were 3 years older. This result could not be attributed to differential mortality, since those who died during the interval were excluded. The South Wales data were more consistent with expectation, the mean of the second measurements of systolic pressure being higher than that of the first, but closer examination showed that this was true only for the Rhondda Fach series. In the Vale of Glamorgan (as in Birmingham), mean pressure did not rise. A possible explanation for these anomalies was suggested by the inverse relationship between temperature and arterial pressure. Retrospective examination of Birmingham meteorological records indicated that air temperatures were in general much higher when the second observations were made than at the first survey (although both readings were made during the summer months). Even greater differences in temperature presumably operated in the Glamorgan survey, since the first was in the winter and the second in summer. Both Rhondda surveys, on the other hand, were carried out during the winter.

The results of these surveys illustrate some of the difficulties which will confront those who try to provide the much needed evidence on the trend of arterial pressure with increasing age in individuals in the general population. In longitudinal study of substantial numbers of subjects (which is needed) it is difficult to do more than record casual pressures. Yet they provide a very unreliable guide to basal pressure and cannot be much improved by refinements of technique which are feasible for use with a considerable random population. Perhaps the most practical, although still difficult, procedure would be to take frequent measurements of casual pressure from which mean values for each individual can be estimated.

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The medical witness

A medical witness may belong to one of three main categories Firstly he may give testimony about hi own treatment of the litigant which makes him rather like other factual witnes es or secondly he may be asked to examine the patient olely with a view to qualifying him elf to give evidence either for the litigant or the opposing party The third typ of medical witness is one who does not or who is unable to examine the patient p rsonally but who is prepared to express his opinions on assumed facts and other scientific data

The first type of witne s appears in court often as a result of subpoena and does o with trepidation and reluctance since he feels quite out of his depth Perhaps n attempt ng to guide the answers he gives toward hi patient s interests he may find that he is given a drubbing by opposing counsel and made to app ar rather foolish With experience the occa sional witnes in addition to answering truthfully and promptly gives the appearance of impartiality which only comes by refusing to be a parti an in the case

The second type of witness often comes from among the younger speciali ts who may eagerly seek this class of work because of its good remunera tion with few or no bad debts It is challenging work and keeps a medical witness *on his toes* by making him delve into the literature in order to be authori tative in court The only pitfall here is when a wit ne goes beyond his specialty This can lead to a mo t unhappy cene in court when one s deficiencies show through under the stre s of a puni hing cross e examination by a determined counsel

The third type of witness is I believe becoming rather rare in America where many speciali t physicians and surgeons try to avoid court appear ances because of painful experiences and because of divergence of the medical and legal viewpoint on what constitutes the truth Even after con iderabl exp rien e the physician gains the impre ion that neither the counsel for the plaintiff nor the counsel for the defendant has any idea of seeking the truth and nothing but the truth but he is only making every effort to win his case [2]

Thi ituation has led to the experiment in New York City of having a medical panel from which are chosen impartial medical witnesses The scheme appears to be operating succe sfully and spreading

Some of the witnesses in this third group are often semiretired specialists a few of whom polarize them selves as plaintiff s or defendant s men and their value as witnesses is soon summed up by the judges Others because of personal research or because of their writings in a pecial field attract work and then run the risk of becoming rubber stamps en dor ing the viewpoints of insurance company medical officers Only scientific integrity will protect them from the temptation to endorse all the work that comes from such big insurance clients

Occasionally too much publicity ■ given to medical witnesses in court but more often than not insufficient notice i taken of bizarre opinions ex pressed by specialist witnesses Sometimes this is pure venality sometimes expediency On very rare occasions we see an innovator at work weaving attractive theories out of the air and giving scientific sounding names to various stages in the process To prove a particular case and to trace its mecha nisms from cause to effect he then proceeds to walk on these fragile steps of verbal imagery as if they were the concrete of reality Their apparent plausi bility may convince juries but less often judges and they operate best where there is a di i ion of opinion among the orthodox These people do the medical profession a great deal of harm by spuriously in vesting it with an image of complete confusion over often fundamental is ues

The Chief Justice of Australia Sir Owen Dixon before his elevation once sagely remarked apropos the ease or difficulty with which a medical witness carried out his task of explaining the medical a pect of a case to the court That it is not when medical *or cientific* conceptions are intricate but when they are vague that the process i troublesome Un fortunately in me licine many conditions have no well defined etiology and this al ows unlimited *scope for legal* argument e pecially if the services of an innovator can be procured

In the state of New South Wales in injury cases or where illness has followed trauma the critical matter for investigation in so many cases is whether or not there is any causal connection between a proved trauma and admitted incapacity or whether trauma has accelerated aggravated or precipitated some pre-existing d sability [3] Causal in

whereas medically it means etiology, and it is over this difference in concept that doctors and lawyers sometimes fail to see eye to eye.

In Workers' Compensation litigation involving cardiac problems the situation takes on an almost lunatic aspect when one is asked to make dogmatic statements on cause and effect when we are grossly ignorant of so many key steps in the mechanisms of ischemic heart disease. It may be accepted, and not unreasonably so from the lay point of view, that courts regard a close relationship of effort to death as being enough for effort to be able to cause an aggravation, acceleration, exacerbation, or deterioration of an underlying diseased heart.

The Report of the Committee on the Effect of Strain and Trauma on the Heart and Great Vessels, 1963[3] tried to give a lead in the difficult problem of work and coronary disease. They found the American situation to be more realistic than that pertaining in Australia—they found *inter alia* that the enquiry of the courts has been directed almost entirely to the question of whether the claimant's previously existing heart condition was aggravated to some extent by stress, strain, or trauma at work. The courts have not made the assumption that a previously healthy person can develop cardiac disease by stress, strain, or nondirect trauma.

On the other hand, one notable example of a legal and possibly the average lay view in this matter was that of Acting Chief Justice (of Australia) Rich, who stated in a particular trial quoted by Larkins: "I am greatly impressed by the sequence of events. The deceased, who had arrived at an age when arteriosclerosis and atheroma affect mankind, was a stevedore's labourer. On the day of his death he climbed up the jib of the crane . . . immediately after performing this task he collapsed. . . . I do not see why a Court should not begin its investigation, i.e., before hearing any medical testimony, from the standpoint of the presumptive inference which this sequence of events would naturally inspire in the mind of any common sense person uninstructed in pathology. . . . Why should not a Court say that *here is strong ground* for a preliminary presumption of fact in favour of the view that the work materially contributed to the cause of death. . . . If medical knowledge develops strong positive reasons for saying that the lay common sense presumption is wrong, the courts no doubt would gladly give effect to this affirmative information. But while science presents us with no more than a blank negation we can only wait its positive results, and in the meantime act on our own intuitive inferences."

One is often asked whether a given amount of effort caused a heart attack. It is generally conceded that if the effort was unduly severe and the symptoms had an immediate relationship to it, there is a case to be made out. Accustomed effort is not usually held to cause a heart attack in the legal sense. Although it is generally conceded that effort cannot cause coronary thrombosis, deaths or infarction can proceed without this event if the relationship is as above. If a man has severe underlying coronary atheroma and the mere shutting of a window induces death, is this work excessive for the individual? If one believes that extra work beyond the capacity of an individual causes coronary insufficiency, then in most cases extra work should cause cardiac pain and warn the individual. In cases of acute emotional excitement, death may occur because the work of the heart increases beyond the capacity of the diseased coronary tree to victual it, or there may be more subtle hormonal factors at work. In some circumstances one would feel that this situation is allowable as a work-caused death under the framework of the Compensation Act as it now stands.

Thus, there is no room for taking up fixed postures in this matter because (1) our true knowledge of the situation is not complete, (2) legal cause and effect differ from medical ones, and (3) compensation acts are social acts, and if the truth be known, the medical witness is not at all the key figure in the situation that he may assume that he is. It is important for medical witnesses to confine themselves to the scientific truth and allow others to interpret this; in other words, they should not try to be both physician and advocate.

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Biochemical differences in the composition of primary varicose veins

The primary role of congenital factors in the etiology of primary varicose veins has been confirmed by Ferovsky and associates.[1] However, exactly what is inherited is not known. Since varicose veins are often found in combination with flat feet, hernia, and hemorrhoids, some inadequacy of connective tissue has been assumed. Therefore, the structure of the venous wall in terms of collagen, elastin

muscle substance and hexosamine (for mucopoly saccharides) was analyzed The first problem was to determine the relative quantities of these sub tances in normal venous walls and for this purpose the internal saphenous vein (ISV) was used since it is most frequently involved with varices Previous findings by Svejcar and a sociates[2,3] have shown a preponderance of collagen in this structure and variou functional parameters determining struc tural changes were analyzed The main study was concentrated on the analysis of varicose veins This was achieved by a comparison of normal vein and primary varicose veins and a further group of normal venous segments from patients with pri mary varicose veins has also been analyzed It i known that primary varicose veins develop slowly and that if varicose ites are removed further varices continue to develop el ewhere The latter group has been labeled potential varicose veins The three types of veins to be analyzed were obtained thus (1) Normal vein (ISV) were removed from cadaver material in which there was no evi dence of varices Two samples were taken one from the proximal segment near to the junction of the femoral vein and the other from just above the ankle (2) Samples of varicose veins were obtained at operation Care was taken to ■ ■ only samples from uncomplicated primary varicose veins None of the patients had trophic changes in the skin or edema Most of thi series also had had no hi tory of phlebitis and there were no signs of po tphlebitic changes in the skin in any of the group (3) Samples of potential varico e veins were al o removed at operation and th re wa no macroscopic evidence of varicose enlargement Varix as well as potential varix material was taken from various segments of the ISV *The techniques* u ed for the determination of collagen elastin muscle and water content and for the *preparation of* dr ed material have been described in detail[3] The chemical method for the connecti ■ tissue *components were based* on the Neumann and Logan procedure The estimation of hexosam ne for mucopolysaccharide was carried out by a modified method for minute samples of tissue derived from the *method of* Ces and Tilsego[7] All differences which were found in the contents of the variou *components were* evaluated stati tically

The main goal of the present work was to compare quantitatively the content of the three ba ic components i e collagen elastin and muscle of the ISV wall in the three categories under study It was found that both actual and potential varicose ve ns contained le s collagen than that in normal ti ue This difference was 15 per cent in the case of vari ose veins and 12 per cent in the ca e of poten t al vari ose veins The defi iency of collagen in the wall of both types of pathologic veins is compen sated for by mu cle ti ue The muscle content of pathologic veins wa increased by 15 per cent in varicose veins and by 12 per cent in potent al vari cose vein At the same time there was only an in i nificant r se m the elastin content in actual and potential aric se vein The differences in the content of collagen and muscle may have a noticeable influence on the qual ty of the venou wall since these two sub tances compose about 90 per cent of the dry matter of the ISV Besides these major findings the mucopolysaccharide hexosamine content was significantly higher in actual and potential varicose vein than in normal veins Primary varicose veins contained 67 per cent more hexosa mine (which compo e about 0 3 per cent of ISV dry material) than that in normal ti sue and potential varices 46 per cent more By serial investigation of samples from one vein a relation hip between water content and mucopolysaccharide hexosamine con tent was determined There was wide variation of water content in varix material in comparison to that in normal and potential varix material which may merely be a reflection of the variation in the degree of varix alteration dealt with In the paral lelism of change in water and hexosamine content there was less catter in the latter and greater sensi tivity of measurement

The above mentioned results indicate that there i a clear difference in the composition of normal veins and primary varicose veins Thi i charac terized by a lower content of collagen and an in crease in the muscle and mucopolysaccharide hexosamine fraction Analy is of longer segments of veins has shown a wide scatter in hexosamine and water content in varicose veins in contrast to the findings of analy i of neighboring segments of normal material Hi tologic stud es have confirmed this As stated above one of the theories of the pathogenesis of primary aricose veins i an in adequacy of connective tis ue in these subjects The finding of a decreased content of collagen and an elevated content of mucopolysaccharide hex osamine in agreement with the anatomy and clinical appearance of varicose vein corroborates this In short the connective ti ue anomaly i not a continuous factor along the length of the vein it is a segmental one It is difficult to say from pure chem cal analysi of these groups which of the differences i primary the decrease in collagen or the increase ■ muscle and hexosam ne However our *election of a potentially* varicose group a ists in uch a differentiation From the clinical point of view primary varicose veins have been considered to be an untreatable disease[4] Very often remo al of varices by operation i only followed by the appearance of variets elsewhere in the lower extremities Thi is the logical ba is of the selection of the third group of veins analyzed The result *show that there were* def nite tructural differences between the normal and potential varicose *groups parti ularly* in terms of collagen and mucopolysaccharides and that the potential varix group was *similar in* composition to the actual varix group So-called potential varix material consisted *of segments of* macroscopically normal vein from individuals with varices elsewhere These segments *were obtained* at operation and neighbored on actual varicose enlargement or were taken from *the junction of the* ISV into the femoral vein in cases in which the same ISV contained more di tal varices These patients showed no incompetence of the saphenous femoral venou valve (The ve n was not palpable when the patient was in the erect posture) The objection may be ■ sed that even if *these* venous segments were macroscopically normal they were subject to abn rmal pressures wh ch

might influence their composition Such changes might then progres to actual varices The answer to this objection could not be given by our finding so that we can merely put forth the hypothesis that the primary defect i in the collagen content of the venous wall A similar change in the wall of a vessel although less marked ha been described by Lorenzen[9] in atheromatou aortas of rabbits which have been given adrenaline and thyroxine A decrease in collagen and an increase in mucopolysaccharides may therefore be non pecific reactions to various parameter Analysis of other venous segments where the effect of high intravascular pressure can be excluded e g from the upper extremities of subjects with varices might contribute information on thi problem Further biochemical analysis of the interrelationships between collagen and mucopolysaccharide metabolism will also be required

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Letter to the Editor

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January 8 1964

To the Editor

Direct-current countershock as described by Dr Bernard Lown[1] has certainly provided a dramatic new method of treatment of various arrhythmias Experience to date would indicate that this is a safe procedure Dr Thomas Killip[2] however has recently described ventricular fibrillation immediately after direct-current countershock This occurred on two separate occasions in one patient The purpose of this communication is to call attention for the first time I believe to an instance of ventricular fibrillation approximately 1 minute after the use of direct current in a patient with atrial fibrillation The shock was given just after the peak of the R wave

The patient a 53 year-old woman had successfully undergone an aortic valvulotomy 6 months previously Shortly after this valvulotomy her atrial fibrillation was converted to a sinus rhythm with quinidine However the arrhythmia recurred and further attempts at conversion with quinidine failed to restore a sinus rhythm She was therefore given 150 watt seconds of direct current while under sodium Pentothal anesthesia with prompt restoration of a sinus rhythm

However she failed to maintain the sinus rhythm and a month later was again given 150 watt seconds of direct current Sinus rhythm promptly resulted although frequent premature beats were present These were also noted after she had received 250 mg of sodium Pentothal prior to the shock Ventricular fibrillation occurred approximately 1 minute after the shock After this had been observed for about 30 seconds she was given another shock of similar quantity which promptly converted the ventricular fibrillation to a sinus rhythm This has been maintained for the past 8 months and she has remained well clinically She is receiving prophylactic doses of quinidine and a maintenance dose of digitoxin

The reason for the occurrence of ventricular fibrillation in this instance is not clear Clinically there was no evidence of overdigitalization She had received 0.4 Gm of quinidine 1 hour before the procedure Likewise there was no clinical evidence of an electrolytic imbalance although she had received small doses of diuretics The electrocardiograms before and after conversion were essentially unchanged except for the change in rhythm No study of sodium or potassium was made

This experience does show that ventricular fibrillation can occur soon after the use of direct current for conversion of chronic atrial fibrillation It also emphasizes the importance of monitoring the patient for some time after the utilization of direct current

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Book reviews

RADIOMETRIE. THEORIE UND PRAXIS RÖNTGENOLOGISCHER MESSMETHODEN. By Dr. Med. Hermann Buchner. Berlin, 1963, Springer Verlag, 165 pages. Price 56 DM.

In the *Vorwort* the author justifies his publication by noting that no complete treatment of the subject had previously been written. *The American* work by Lusted and Keats (*Atlas of Roentgenographic Measurement*) says Buchner, is too limited: it omits transillumination methods and as for cardiac size (including volume) deals only with American techniques based on the single plane sagittal area. The author himself proposes to examine the entire field of measurement by means of roentgen rays (das *gesamte Gebiet des Messens mit Röntgenstrahlen*) but intends to give short shrift to techniques that are solely of theoretical interest.

Quantitative roentgenology, the author tells us, really began in the first few years after 1895 and it was the cardiologists in particular who gave it impetus. There follow very reasonable chapters and reference lists on distortion and principal means of obviating it, on localization of objects and lesions and on mapping of deep lesions.

Sections on estimation of cardiac size and on determination of cardiac volume are routine and undistinguished. Standard methods of measuring frontal and sagittal plane diameters are presented and orthodiametry is discussed critically and in very considerable detail. The *treatment of cardiac volume* determination begins with a review of contributions, mainly German, which are based on formulas involving one or more measurements from roentgen films. Then the account deals *in extenso* with Buchner's own method, originally based on modifications of the Rohrer-Kahlstorf formula but now based on the use of four projections so selected as to permit the best definition of the cardiac shadow (roentgenography). The method requires that a lead marker tape be put around the patient's chest about the mid point of the patient's heart. One diameter near the mid point of the heart is then determined from the four points for the chosen level which the four films provide (in the case of a P A film, two are posterior, two anterior). These points are then placed accurately on an outline of the circumference of the chest (to which the numbers on the marker tape have been transferred) at the level of the diameter in question. Values obtained from the three other films are then treated comparably, so that one can finally locate eight points of the cardiac diameter and connect them (presumably free hand). Then 1 cm below the measured diameter a second diameter is measured off and its circumference estimated similarly. The same procedure is repeated at 1-cm intervals above the original. In this way about a dozen circular or elliptical figures are obtained, the areas of which are measured planimetrically. After proper correction the observer has at hand ten or a dozen sections of the heart (all chambers) each 1 cm thick, the volumes of which are known (area in square centimeters × 1.0 cm). The total of the volumes is the volume (in milliliters) of the heart. The method lends itself to the construction of models of the heart which, according to the author, can be used to check the accuracy of the method above.

The rest of the volume deals with orthopedic and obstetrical applications as well as measurements of the skull, delineation of tumors and localization of foreign bodies, all of which are outside the scope of this review.

The book is very well illustrated and is beautifully printed on good stock. Its lists of references are especially useful although they are grossly incomplete with regard to the English and American literature. The discussion of methods of measurement of cardiac size is useful as a review provided that one reads highly involved tautologic German. The author's own method for measuring cardiac volume is in principle identical with that published from this reviewer's laboratory in 1958 (*Circulation* 18:1105-1117, December 1958) but apparently not available to Buchner. The earlier method devised for use with biplane cineangiographic equipment permits the application of a scanner computer with the result that much of the tedium and inaccuracy is obviated. It provides a series of individual ventricular volumes or biventricular volumes as frequently as every thirtieth of a second and some more recent cineangiographic methods using the same principle do even better. Buchner's method, however, can provide only one or two volume measurements (e.g., systolic and diastolic) and obviously requires many hours of tedious and largely unrewarding labor for a very limited end result.

In short, Buchner's volume is not likely to be of much interest to the cardiologist or internist nor is its content really up to date with regard to measurement of cardiac or chamber volumes, an area in which cineangiographic methods are now taking over. The book will obviously be of interest to the röntgenologist and may serve to call attention once more to the usefulness of roentgenography as a quantitative tool.

CALCIFICATION OF THE HEART. By Joseph Jorgens, M.D., Ph.D. Springfield, Ill., 1963, Charles C Thomas, Publisher, 198 pages. Price $12.50.

This monograph is a presentation of the author's material on cardiac calcification and a review of the literature on the subject. The discussion and review of the literature emphasize the radiologic aspects, but clinical and pathologic references and viewpoints are presented. The clinical and pathologic discussion will probably be considered to be sketchy and unsophisticated by the cardiologist.

The book is divided according to the site of the calcification e.g. one chapter is devoted to *calcification in the coronary arteries* another to calcification in the patent ductus etc. No calcifications outside the heart are considered. The first part of each chapter includes the discussion of the literature and the author's material whereas the last part is a series of illustrations of x-ray films of living patients and autopsy material. These are excellent reproductions and represent the most valuable contribution of the monograph.

The chapter on calcification in the valves is of most widespread practical interest and occupies almost half the book. A large number of excellent illustrations is included. The presentation is confusing because of the failure to clearly separate aortic calcification per se from calcific aortic stenosis in the discussion and references pertinent to both are intermixed indiscriminately. The chapter concerns itself only with calcification of the aortic and mitral valves.

The last chapter is a discussion of cineradiography, the recording of motion pictures of the cardiac movement on the image intensified fluoroscopic screen. The author believes that this is the best technique for the detection of cardiac calcification.

The monograph is recommended largely for its series of excellent illustrations but most readers will find the discussion and presentation of the author's material also helpful.

DIFFERENTIALDIAGNOSE KONGENITALER HERZFEHLER (Differential Diagnosis of Congenital Heart Disease. Synopsis of Radiography, Electrocardiography and Phonocardiography.) By Nikolaus Schad, Ralph Kunzler, and Teoman Onat. Stuttgart 1963 Georg Thieme Verlag 450 pages. Price 99DM.

In their 450 page monograph Schad, Künzler and Onat attempt to correlate the radiographic, electrocardiographic, and phonocardiographic findings in congenital heart diseases of children.

The book is divided into two parts. The first part (26 pages) is devoted to the general discussion of radiographic examination of the heart. The second part, which comprises the remainder of the monograph, is subdivided into four sections.

The first section is concerned with the hemodynamic changes in various congenital heart diseases and their effects on heart chambers, aorta, and pulmonary vessels.

The radiographic, electrocardiographic, and phonocardiographic criteria for the differential diagnosis of congenital heart diseases are discussed in the second section.

The radiographic, electrocardiographic, and phonocardiographic findings in various congenital heart diseases are presented in the third section.

Miscellaneous heart diseases such as endocardial fibroelastosis, glycogen storage disease, anomalous origin of coronary arteries, myocarditis, pericarditis, tumors of the heart, etc. are briefly discussed in the final section.

The reference list is up to date and the index is good.

The monograph is aimed at the clinical cardiologist. The reproduction of pictures and tracings is excellent. There is some degree of oversimplification in the diagrams related to the radiographic changes in various congenital heart diseases. The angiocardiographic studies are done from the right ventricle or pulmonary artery only. The monograph does not contain selective angiocardiograms from the left ventricle or retrograde aortograms. There is no adequate documentation of diagnoses of the cases presented. Pathologic specimens would have been preferable to clinical diagnoses.

The value of phonocardiograms would have been markedly increased by including other references such as carotid pulse recording, apex cardiogram, etc. in addition to the electrocardiographic Lead II which the authors have taken as the only reference.

In spite of the above-mentioned limitations the monograph represents an instructive collection of information which should prove to be useful to the clinical pediatric cardiologist.

KLINISCHE RÖNTGENDIAGNOSTIK INNERER KRANKHEITEN I THORAX (Clinical Roentgen Diagnosis of Internal Diseases Vol. I). Edited by Richard Haubrich with contributions by H. Anacker, R. Haubrich, K. Heckmann, A. Schaede, and H. St. Stender. Berlin 1963 Springer 708 pages 746 illustrations. Price 220 DM.

This German monograph is the first volume of a comprehensive treatise on the diagnostic roentgenology of internal diseases. The title is similar to that selected for a similar two-volume series published by Assmann in 1950.

The first volume on the thorax has major subdivisions on diseases of the heart, great vessel, lung, pleura, mediastinum, and diaphragm. Method of examination and roentgen findings in individual diseases and disease groups are presented. Disease processes are discussed in an orderly manner with classification similar to that employed in standard texts on internal medicine and diagnostic roentgenology.

For example in the section on the heart generalized cardiac enlargement and enlargement of individual chambers are discussed following which the specific findings in various acquired and congenital cardiac diseases are presented. Numerous excellent diagrammatic sketches and roentgenographic reproductions add greatly to the text.

Considerable stress is placed on the pathologic anatomy and physiologic basis of the roentgen signs. This creates a bridge of understanding between the internist, surgeon, and roentgenologist.

It is difficult to criticize this work in a negative way. Many American readers still have difficulty with positive roentgenographic reproductions. However, patient study of the excellent reproductions in this volume will be very

Book reviews

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In the *Vorwort* the author justifies his publication by noting that no complete treatment of the subject had previously been written. The American work by Lusted and Keats (*Atlas of Roentgenographic Measurement*) says Buchner is too limited; it omits transillumination methods, and as for cardiac size (including volume) deals only with American techniques based on the single-plane sagittal area. The author himself proposes to examine the entire field of measurement by means of roentgen rays (das *gesamte* Gebiet des Messens mit Röntgenstrahlen) but intends to give short shrift to techniques that are solely of theoretical interest.

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Editorial

Isotope clearance and myocardial blood flow

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Radioisotope techniques for the study of the circulation have evolved at a progressively accelerating rate during the 35 years since the earliest semiquantitative estimates of the linear velocity of blood flow were made with radium C and a Wilson cloud chamber.[1] A wide variety of techniques have followed which are also based on the use of externally placed detectors to record the flow of an intravascular bolus of radioisotope through the body. Methods of quantitation have been developed that are based on adaptation and expansion of the indicator dilution concepts of Stewart, as developed by Hamilton and others. The use of the Fick calculation and clearance concepts has provided another major avenue of approach. The speed of clearance of injected tracer *from* a site of injection is closely related to the volume rate of blood flow to the area.[2] However, the results are difficult to quantitate in terms of blood flow, even "effective" blood flow, and this technique is not easily applied to the viscera of man. The entrance of isotopes *into* tissue cells from the circulating blood has also been made the basis for measurements of regional blood flow.[3] This general approach is readily applied to the heart because there is a rapid exchange of potassium ions across the myocardial capillaries and cellular membranes and a large reservoir of potassium within the muscle cells. More than one half of any K^{42} or Rb^{86} in coronary arterial blood enters the cardiac cells, from which it returns only slowly to the blood stream. Since the radioactivity of the human heart can be assessed by external monitors, the possibility of evaluating coronary blood flow by innocuous methods has been of widespread interest. Unfortunately, the dynamics of Rb^{86} and K^{42} exchange are complex, and their speed of uptake by the myocardium is only partly determined by the volume rate of coronary blood flow. Therefore, there is a real possibility that the results of isotope uptake studies may be seriously misinterpreted.

When a plateau concentration of isotope is maintained in arterial blood by infusing Rb^{86} at a progressively decreasing rate, the behavior of the myocardium toward the tracer can be analyzed as if it were exchanging with an infinite pool of tagged blood. During the first minute of isotope infusion, an amount of potassium equal to more than three times that present in the interstitial fluid of the heart is delivered

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to the myocardium by the coronary blood and almost all of it exchanges across the capillary membrane. A near equilibrium between interstitial fluid and capillary contents is reached rapidly. Thereafter uptake by the myocardium is dominated by the passage of tracer into the cells. It has been shown that during this cellular phase the fraction of the isotope removed from coronary blood during one passage through the myocardium is inversely related to the rate of coronary blood flow.[4] At average normal rates of flow, approximately two thirds of the tracer is removed. The fraction entering the cells can be looked upon as being determined by the ratio of the amount of K entering the cells to the total of the amount entering the cells and the amount leaving the interstitial fluid in the effluent blood. At each rate of cell ion flux there is a unique and nonlinear relationship between blood flow and isotope clearance. Changes in flow, therefore, tend to be somewhat offset by changes in the ratio of the tracer extracted from blood, but the compensation is only partial. When the myocardium is allowed to take up isotope over any known interval of time, there is a characteristic amount of blood cleared of isotope for each rate of flow. Individual differences in intramyocardial hemodynamics and metabolically determined cellular ion fluxes undoubtedly occur normally, and they may result from differences in pulse rates, anoxia, or the effects of some drugs.[5] These and other factors produce variations around the mean relationships of flow and clearance. However, in the data obtained on dogs to date, such variations have been relatively minor.[4] They probably will not seriously interfere with the relationship of blood flow and isotope clearance in man under the usual clinical conditions, although this remains to be established. Differences in plasma potassium concentration have not been shown to affect the isotope uptake process. However, it seems likely that the speed of equilibration of the cellular compartment will be inversely related to the cellular potassium concentration and possibly directly related to the plasma potassium concentration. This would affect the rate of return of tracer from the cells to the blood and, therefore, the total isotope uptake over any appreciable length of time. The effect would be greater the longer the interval, i.e., the greater the total amount of flow during the interval studied. The amount of potassium present in the cells is approximately 40 times the normal amount brought to the myocardium by the circulation in 1 minute. This large cellular potassium pool, which tends to limit the early return of isotope from the cells, is probably very important in minimizing the effect of potassium concentrations on the relationship of blood flow and isotope clearance. It is clear that as equilibrium between plasma and myocardium is approached, the tracer content of the heart may be determined more by nontracer concentrations than by blood flow. Infarcted or severely ischemic muscle has a low potassium concentration, which would tend to promote confusion. Diffusion of the isotope over appreciable distances within the myocardium may play some role in isotope distribution, although this has not been demonstrated. Diffusion would probably be particularly evident at the margins of poorly vascularized or necrotic areas. Direct passage of the tracer through the endocardium from the heart cavities is another possibility.[7]

Much of the data to date has been obtained with isotopic rubidium because of the convenient half life of Rb^{86}. Rubidium is known to resemble potassium closely in its effects on the heart, and Rb^{86} accumulates in proportion to the potassium concentration gradients in the myocardium.[8] Cesium is somewhat similar to potassium and rubidium, and radiation from Cs^{131} offers some advantages for external detection.[9] However, dynamics defined with one element obviously do not necessarily apply to others. The situation must be separately defined for each tracer.

When K^{42} or Rb^{86} is injected rapidly intravenously as a single bolus, the tracer content of many organs, including the canine and rat hearts, rapidly reaches a high counting level and remains at a plateau for many minutes—despite a rapid fall in blood levels. It has been reasoned that the portion of the injected isotope that is taken up by the heart during this early period is equal to the fraction of the total

cardiac output which reaches the myocardium.[16] Reasonable values for coronary blood flow have been obtained in experimental animals and recently this approach has been modified and applied to man.[11] Much more extensive data are required to evaluate the reliability of this method both in man and experimental animals.

The technical problems in quantitating internal distribution of isotope by use of external detectors are common to all methods applicable to man. Initial studies relied on inferences based on the time course of changes in counting rates over the precordium and adjacent areas which were monitored during an initial period and at the end of 24 hours.[1] Heavy shielding is necessary with Rb^{86} since more than 10 per cent of the 1.08 mev. gamma radiation will pass through 1 inch of lead. Approximately 5 to 10 per cent of the isotope infused enters the myocardium and a much larger total amount is present in the adjacent tissues, especially the liver. Restriction of counting to the annihilation radiation of Rb^{84}, a positron emitter, simplifies the shielding and can improve collimation.[12] Parallel studies with I^{131} albumin may provide a means of distinguishing radioactivity in blood from that in the myocardium—a particularly important problem when the bolus type of injection is used.[13]

The characteristics of myocardial potassium exchange enable studies to be made in experimental animals which differ significantly from those possible with other techniques. The Fick approach can be applied directly to any area of the myocardium from which representative venous blood can be obtained. Calculations of blood flow are made from the integrated arteriovenous difference in isotope concentration and the radioactivity of the tissue measured after the animal has been killed at the end of the period of study. Total flow per unit of tissue during the period of isotope infusion is measured, rather than the flow through one particular vessel or the flow per gram of tissue reaching equilibrium during the study period. Data obtained in this way have shown, for instance, that blood flow per unit weight of the right ventricle in the anesthetized dog is substantially less than that of the left ventricle.[14] When the investigator is willing to rely on the mean relationship of rates of blood flow and isotope clearance in the interpretation of the results, or wishes to consider regional rates of isotope clearance as minimum rates of flow, it is possible to compare regional flow rates in separate areas of the myocardium while avoiding the experimental restrictions required for collection of venous blood from the heart. In this way, flow to the atria has been estimated and found to be approximately the same as that in the right ventricle. The inner and outer parts of both ventricles have been discovered to have varying differences in their rates of isotope uptake. Although detailed study and mapping of such regional patterns has only begun, the results to date have uncovered areas in the right ventricle in which there are unexplained elevations of Rb^{86} clearance.[15] Simultaneous comparison of flow in one part of the heart with that in another offers a new approach to the study of the coronary circulation. Such data will inevitably add to the understanding of the mechanisms which control the regional distribution of coronary blood flow.

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Clinical communications

Circulation times in patients with neurocirculatory asthenia

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Neurocirculatory asthenia (Da Costa's syndrome, effort syndrome, etc.)[1,2] has been recognized as a distinct ill-defined condition of the heart and circulation of neurogenic or psychogenic origin. Its frequency is known to cardiologists and general practitioners. In our patients this disease amounts to about 22 per cent of all cardiac disorders.[3] Da Costa's syndrome has a rather typical symptomatology; however, the physical signs are more ambiguous and objective tests are not unanimously accepted.

During studies on circulation times with the dye method[4,5] and with gaseous indicators,[6] we observed certain circulatory abnormalities in patients with neurocirculatory asthenia which proved to be significant on statistical evaluation.

Methods

Twenty patients who had the characteristic anamnesis of Da Costa's syndrome and 20 control subjects who had no cardiovascular disease were considered to be comparable with regard to their ages, heights, weights, pulse rates, and blood pressures. The group of patients was comprised of 15 females and 5 males, whereas in the control group there were 8 females and 12 males.

The circulation times were determined with the dye method using methylene blue. The instant of injection of dye as well as the appearance at the end point were measured photoelectrically; in this way the method was completely objective. Details are described elsewhere.[5] Two circulation times were recorded simultaneously with an ear unit and an extremity unit*: (a) the left arm to right ear time (AET) or "central" circulation time and (b) the left arm to left foot time (AFT) or "peripheral" circulation time.

All tests were done with the control subjects in a supine position and in a thermoindifferent environment.

For statistical evaluation the following formulas were used:

Standard deviation

$$(s) = \pm\sqrt{\frac{1}{n-1} S (x - \bar{x})}$$

Standard deviation of the means

$$s_m = \pm \frac{(s)}{\sqrt{n}}$$

For evaluation of the significance of the difference of the two means (Student t test)

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s_D} \qquad s_D = S\sqrt{\frac{n_1 + n_2}{n_1 n_2}}$$

$$S = \sqrt{\frac{S_1(x - \bar{x})^2 + S_2(x - \bar{x})^2}{n_1 + n_2 - 2}}$$

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Results

Table I summarizes the data i e age sex blood pressure (after Korotkoff) weight (kg) height (cm) pulse rate during the test and the circulation times of the normal group Table II summarizes the corresponding data of the patients with neurocirculatory asthenia

The fact that the means of weight and height are slightly smaller in the group of patients with neurocirculatory asthenia is due to the preponderance of females in this group The average age does not vary significantly The mean arm to ear time of the control group is 10 4 second with a standard deviation s = ±1 64 This value is in agreement with the figures of others [8, 11] The mean arm to foot time of 26 9 seconds also corresponds well with the findings reported by others [19]

As shown in Table II the arm to ear time of the patients with Da Costa s syndrome is slightly prolonged but does not differ statistically from the figures for the control group However the arm to foot time of the patients is markedly lengthened The mean AFT is 46 9 seconds s = ±10 5 The arm to foot times of both groups differ significantly p smaller than 0 01

Discussion

There are several methods used for the measurement of circulation times Some are of interest only from the historic viewpoint since these do not provide an accurate and objective determination of the end point More recent methods use dyes with certain optic qualities radioactive substances or gaseous indicators [1] which are bound either to the erythrocytes or the blood plasma It is recognized that the velocity of the red blood cells is faster than that of the plasma flow

Since the first application of the oximeter for continuous recording of the concentration of indicator in the flowing blood [13] this method has proved to be rather valuable in the diagnosis of congenital and acquired heart disease [16, 17] and in the measurement of the cardiac output [15] The determination of circulation times with the oximeter and dye method was first described by Matthes [18] who employed an oximeter which detected light in two spectral regions red and infrared The same photoelectric principle was used in these studies We used a higher dosage of methylene blue as is recommended i e 30 mg per injection sparing the oxygen breathing of the patient [8] With synchronous measurement of different circulation times in one subject differentiation of circulatory states close to the heart (central circulation time) and those mainly referable to the peripheral blood flow (peripheral circulation time) is possible In the case of obstructive lesions of the extremities peripheral circulation times should be prolonged whereas in heart decompensation the central circulation time is lengthened

The dependence of circulation times on age [8, 9] pulse rate [7] position of the body [1] temperature [2] and body surface [3] has been described previously Pathologic conditions such as anemia Paget s disease Graves disease etc shorten the circulation time whereas other conditions such as hypothyroidism heart decompensation and polycythemia prolong the circulation time

These factors—in particular hypothyroidism and heart failure—were looked for and could be excluded in this study As can be seen from Tables I and II other elements which could have a bearing on the circulation time (age pulse rate body surface weight and height) do not differ significantly in the two groups

With regard to the *central circulation times* (arm to-ear time) we noted a slight prolongation in the patients with Da Costa s syndrome Even taking into account the smaller means of height and weight of that group this difference proved not to be significant statistically

The *peripheral circulation times* (arm to foot time) showed a marked divergence between the control group and those who were suffering from neurocirculatory asthenia The corresponding figures of the means are 26 9 and 46 9 seconds which is in agreement with a recent study [10] This signifies an average prolongation of the arm to foot time of about 75 per cent in patients with the Da Costa syndrome in comparison to that of subjects who have no cardiovascular abnormalities The difference in sex distribution in the two groups cannot account for this phenomenon (compare the 8 females of the control group

Table I Data in control subjects

	Name	*Sex*	*Age (yr)*	*B P (mm Hg)*	*Weight (Kg)*	*Height (cm)*	*Pulse rate*	*AET (sec)*	*AFT (sec)*
1	H Z	M	38	1?0/80	7?	180	82	11 ?	25 [illegible]
2	A A	M	32	110/80	54	165	80	, 4	20 0
3	C H	F	21	135/80	66	163	69	9 2	22 0
4	S W	M	30	135/85	78	178	81	12 8	27 6
5	H J	F	42	135/,0	71	1,0	81	10 4	20 8
6	E H	F	26	130/90	7?	168	78	12 4	36 4
7	U K	M	?2	140/80	66	171	98	9 6	26 0
8	J U	M	37	150/90	62	165	81	11 0	30 0
9	F L	F	42	125/80	69	165	80	10 6	21 5
10	I H	F	20	125/80	56	180	83	10 6	?2 6
11	O K	M	39	150/90	76	163	78	9 4	32 0
12	A S	M	5?	150/85	,9	170	86	11 6	35 4
13	H B	M	52	1?5/80	80	1,8	63	10 6	26 5
14	K B	M	27	135/80	,4	177	73	10 6	35 4
15	F K	M	54	110/70	68	166	[illegible]	12 2	24 4
16	L P	F	36	110/80	63	161	74	13 8	35 0
17	E M	F	36	130/80	72	169	84	9 6	21 8
18	D L	M	20	110/80	6?	168	,2	8 6	34 6
19	H B	M	15	120/70	54	168	8?	9 0	18 [illegible]
20	R K	F	2?	105/80	45	160	90	8 2	23 2
	Means		33 2	96 2	66 95	169 5	80 0	10 4	26 9
							(s) =	± 1 64	± 5 98
							=	± 0 38	± 1 35

Mea blood press re = d tol c blood pr ssu e pl e th d of p lse pr ure

Table II Data in patients with neurocirculatory asthenia

	Name	*Sex*	*Age (yr)*	*B P (mm Hg)*	*Weight (Kg)*	*Height (cm)*	*Pulse rate*	*AET (sec)*	*AFT (sec)*
1	S K	F	36	100/,0	60	165	7?	9 9	52 6
2	A H	F	37	130/85	[illegible]	168	77	9 0	49 0
3	C M	F	31	115/80	66	159	,0	10 4	44 2
4	M K	F	33	120/80	51	15,	72	9 4	33 2
5	E P	F	30	105/75	72	168	66	11 8	59 2
6	G F	M	17	110/80	74	176	63	10 6	54 0
7	H S	F	[illegible]	125/80	66	1?3	98	9 2	50 4
8	G B	M	38	145/90	85	174	81	11 0	6? 0
9	F S	F	44	130/80	63	161	74	11 6	40 2
[illegible]	E F	F	19	150 80	85	177	99	8 0	46 [illegible]
11	E S	F	43	130/85	55	151	84	7 6	24 4
12	R W	M	31	120 80	75	184	63	19 0	68 0
13	J F	F	57	100/70	50	158	7?	13 4	50 6
14	I S	F	27	105 70	45	155	93	9 2	45 2
15	G K	F	34	120/90	65	16?	105	6 0	34 [illegible]
16	H L	F	18	110 70	54	158	74	12 8	4? 0
17	I S	F	37	150 90	?2	165	73	10 0	40 6
[illegible]	R B	F	40	120 80	54	158	108	11 0	59 5
19	J G	M	38	135 90	75	172	67	15 2	47 4
20	E W	M	14	1?0/75	53	164	76	8 6	36 0
	Means		3? 2	93 7	64 4	164 7	,9 8	10 7	46 9
							( ) =	± 1 45	± 10 5
							s_m =	± 0 33	± 2 38

Mean bl od press re = diastol blood pressure pl one th d of pulse press

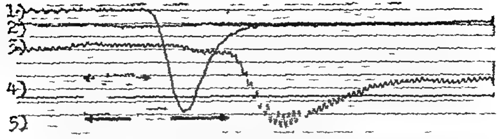

Fig 1 Normal person Dye-dilution curves recorded with an ear-oximeter and extremity oximeter Appearance of dye at right ear at 11 2 seconds after injection at left foot after 25 second 1 Ear-oximeter 2 ECG 3 Extremity-oximeter 4 Marking for injection of dye 5 Time meter AET Arm to-ear time AFT Arm to foot time

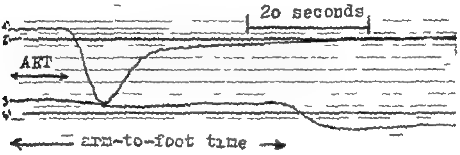

Fig 2 Patient with neurocirculatory asthenia Arm to-ear time 10 4 second arm to-foot time 44 2 second The latter is markedly prolonged

Table I with the 15 female patients Table II)

We concluded that the slowing of the peripheral blood flow in patients with neurocirculatory asthenia was due to a

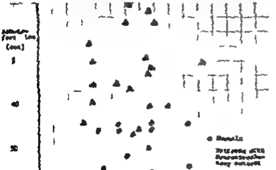

Fig 3 Arm to-foot times of patients with neurocirculatory asthenia and of the control group of normal subjects with no cardiovascular abnormalities

specific and essential alteration of blood kinetics Whether prolongation of the peripheral circulation time affects the cardiac output according to Vierordt s formula has to be evaluated

The slowing of the peripheral blood flow (bradycirculation) should be best demonstrated employing fully objective methods for measuring circulation times To what extent bradycirculation can explain the symptomatology of the Da Costa syndrome is not known Such symptoms as cold hands paresthesias (i e tingling and numbness) acrocyanosis etc could be caused by the supplying of the periphery with a less than normal volume of blood per time unit In contrast to the bradycirculation in neurocirculatory asthenia we found an acceleration of the peripheral blood kinetics in hyperthyroidism

Summary

Synchronous photoelectric measurements of the arm to-ear and arm to foot times were made in two comparable groups one group of normal individuals (n = 20)

and another group of patients with neuro circulatory asthenia (n = 20) The mean arm to-ear times did not differ significantly whereas the mean arm to foot times (peripheral circulation times) demonstrated a marked divergence which proved to be significant on statistical evaluation (p smaller than 0 01) This abnormal slowing of the blood flow should be considered to be characteristic of neurocirculatory asthenia To what extent the pathophysiologic behavior does explain the symptomatology of that disease must be investigated further

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Fig. 2. Case 2. Atrioventricular conduction system schematically drawn on opened right atrium and ventricle. The patch closes the ventricular septal defect. The symbols have the same meaning as those used in Fig. 1.

forming a short arc. The right bundle branch then turned rather sharply apexward so that its fibers were viewed in longitudinal section (Fig. 3,*f*). As a result of this course, the right bundle branch was no longer *closely related to the ventricular* septal defect. In some sections focal hemorrhages were observed in the common bundle and the right bundle branch.

Case 3. The heart in this case exhibited severe subpulmonary stenosis in addition to origin of both the aorta and the pulmonary artery from the right ventricle. The posterior boundary of the large ventricular septal defect was formed by the tissue of the septal leaflet of the tricuspid valve and the anterior leaflet of the mitral valve.

The A-V node was located in an essentially normal position. The common bundle passed through the tricuspid valvular a... immediately after its origin from the ... In its penetrating portion, Mahaim fi... were given ... the bundle to the ... jacent se... After penetr... ing the valv... lle was close ... the left side of the septum at the posterior superior angle of the ventricular septal defect where the left bundle branches were given off. The left bundle branch fibers arborized over the ventricular sep*tum posterior and inferior to the defect.* Those left bundle branches extending apexward were close to the posterior rim of the defect. The right bundle branch followed the curved posterior rim of the ventricular septal defect in the form of an arc. It lay near the center of the septal myocardium. At the posterior inferior angle of the ventricular septal defect, the right bundle branch continued its oblique inferior and anterior direction so that it was no longer closely related to the defect. Thus, the location and course of the conduction system in this heart were essentially the same as that in Case 2.

... examples of origin of the ... the right ventricle with ... stenosis (Cases 1 and 2) ... urse of the major por...

tions of the atrioventricular conduction system were similar in that either the common bundle or the right bundle branch or both lay posterior (dorsal) to the ventricular septal defect (Figs. 1 and 2). This location of the conduction system was similar to that described in cases of ventricular septal defect of the persistent common atrioventricular canal type.[4] The similarities of the electrocardiographic findings and the position of the ventricular septal defect in the three conditions—origin of both great vessels from the right ventricle with ventricular septal defect without pulmonary stenosis, persistent common atrioventricular canal, ventricular septal defect of persistent common atrioventricular canal type[4]—have been pointed out. The deviation of the conduction tissue from its usual course,[3] apparently caused by the presence of the ventricular septal defect,[5] might be the explanation for the observed electrocardiographic abnormalities.

In the cases without pulmonary stenosis the peculiar electrocardiographic findings are explained by the unusually long course of the common bundle. The case with pulmonary stenosis showed essentially the same relationship between the ventricular septal defect and the conduction system. Yet the electrocardiographic pattern was

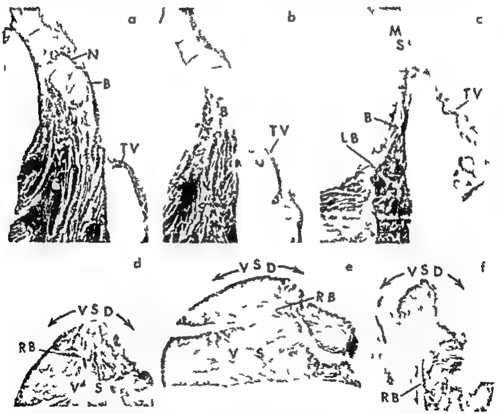

Fig. 3. Case 2. Selected serial sections of the atrioventricular conduction system. *a*, A-V node (N) and portion of common bundle (*B*) in floor of right atrium adjacent to fibrous valvular ring. *TV*, Tricuspid valve. *VS*, Ventricular septum (Mallory-Heidenhain stain ×9). *b*, Common bundle (*B*) passing through fibrous valvular ring (Mallory-Heidenhain stain ×9). *c*, Origin of a left bundle branch (*LB*) from common bundle (*B*) in remnant of membranous septum (*MS*) at posterior rim of ventricular septal defect (Mallory-Heidenhain stain ×9). *d*, Right bundle branch (*RB*) central in ventricular septum (*VS*) and along posterior rim of ventricular septal defect (*VSD*) (Mallory-Heidenhain stain ×9). *e*, Right bundle branch (*RB*) follows curved posterior inferior rim of ventricular septal defect (*VSD*). This section is approximately 3.0 mm. more anterior in the heart than the section shown in *d* (Mallory-Heidenhain stain ×9). *f*, Right bundle branch (*RB*) turns upward beneath inferior rim of ventricular septal defect (*VSD*) (Mallory-Heidenhain stain ×9).

different from that in the two cases without pulmonary stenosis. The difference remains unexplained.

Summary

The locations of the A-V node, common bundle (bundle of His), and proximal portions of the right and left bundle branches were studied in three cases in which both great vessels originated from the right ventricle with ventricular septal defect; one of these cases exhibited subpulmonary stenosis. In all three hearts, conduction tissue lay posterior (dorsal) to, and was displaced by, the defect. The position of the conduction system in the two examples without pulmonary stenosis appeared to be responsible for the reported electrocardiographic abnormalities. The relationship between the conduction tissue and the ventricular septal defect was about the same in the three cases. Yet the electrocardiographic features of the case with pulmonary stenosis were different from those of the cases without pulmonary stenosis. The differences remain unexplained.

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The effects of "dry" heat on the circulation of man Coronary hemodynamics

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In previous communications we have documented the effects of 2 hour exposure to a relatively dry warm environment (98 F 40 per cent relative humidity) on the general[1] splanchnic[2] and renal[3] hemodynamics of normal resting man as well as man with heart disease involving the left ventricle The significant findings in all categories of subjects were decreases in the systemic pulmonary splanchnic and renal vascular resistances principally predicated on significant decreases in the arterial blood pressure with little or no alteration in the observed blood flows The calculated work of the left ventricle likewise decreased[4]

The object of this communication is to present and comment on data similarly collected and relating to coronary blood flow and myocardial metabolism as determined by coronary sinus catheterization in intact resting man

Materials and methods

Thirty two male and female patients were investigated consecutively as they became available from the general medical wards They were divided as follows (8 subjects in each category)

Group A Double controls These patients were free of heart disease having convalesced from various acute illnesses Two sets of determinations were obtained at an interval of 2 hours in the comfortable environment only (73 F relative humidity 40 per cent) These data served as a comparative control for the methodology which was employed

Group B Subjects free of heart disease

Group C Subjects with enlarged left ventricles who were *not* in left ventricular failure (resting pulmonary wedge pressures less than 10 mm Hg)

Group D Subjects with enlarged left ventricles who were assumed to be in left ventricular failure (resting wedge pressures above 12 mm Hg with pulmonary end diastolic pressures above 12 mm Hg) None of these subjects were in right ventricular failure as evidenced by peak end diastolic right ventricular pressures not exceeding 8 mm Hg None of the 32 patients were febrile or anemic

Studies were performed with the pa

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Table I Individual data for 8 subjects with normal hearts in whom all determinations were made at 73° F and 40 per cent humidity

Patient Age (yr)	Race Sex B S	Diagnosis		Heart rate	PBA	CBF	AVD	LVMRO₂	% EXT	CVR
F J	W M	Epilepsy	C	71	131/76 (104)	158	9 21	14 6	58	0 66
60	1 60		2 hr	67	141 80 (108)	118	10 38	12 2	65	0 92
B T	N F	Hypertension mild	C	10?	166/85 (116)	164	9 55	15 ?	59	0 71
58	1 59		2 hr	99	206/106 (149)	187	9 81	18 7	60	0 80
L S	N F	Diastolic hyperten sion with cardio megaly	C	99	179/113 (147)	185	11 59	21 4	76	0 ?9
44	1 78		2 hr	80	212/126 (16?)	155	11 91	18 4	77	1 05
O H	N M	Remote CVA no	C	63	125/87 (104)	42	13 63	5 7	65	2 47
49	1 46	cardiomegaly	2 hr	61	137/93 (111)	46	11 99	5 5	59	2 41
A G	N M	Bronchopneumonia	C	78	115/59 (83)	90	11 41	10 3	65	0 92
67	1 47	recovered	2 hr	69	129/66 (95)	110	11 49	12 6	66	0 86
J K	W M	Wernicke s enceph	C	69	124/83 (102)	108	9 17	9 9	67	0 94
65	1 76	alopathy	2 hr	64	138/89 (110)	147	9 55	14 0	65	0 75
R B	N F	Bronchopneumonia	C	74	139/85 (112)	107	10 91	11 7	69	1 05
32	1 81	recovered	2 hr	82	157/97 (123)	75	11 75	8 8	74	1 64
J D	N M	Inadequate per	C	57	144/87 (107)	116	10 84	12 6	76	0 92
59	1 64	sonality	2 hr	48	146/90 (110)	134	10 53	14 1	75	0 82

PBA B a l l (n l p ssu (mm Hg) the mean p essu g en n pa enthese CBF C nary (left ent ular) flow (c/100 G in n) AVD Arterial- nary sinu xygen d ffe ence (v p) LVMRO Left v ntr cul xygen ut l at on (c c 100 Gm / n) % EXT Myocardial xyg n extra n (a v) CVR C ary vascula esistan e (PBA CBF) C nd h D t m n t bt ed n t ally nd t the end I 2 h urs espect ely

Table II Individual data for 8 subjects with normal hearts

Patient Age (yr)	Race Sex B S	Diagnosis		Heart rate	PBA	CBF	AVD	LVMRO	% EXT	CVR
J B	W M	No disease	C	69	1?2/73 (99)	148	13 23	19 6	61	0 69
46	1 60		2 hr	81	100/64 (83)	124	12 87	16 0	75	0 67
J I	W M	Chronic alcoholism	C	8?	128/80 (10?)	88	11 57	10 2	78	1 16
46	1 78		2 hr	88	106/77 (90)	80	9 48	7 6	62	1 13
B I	N F	Chronic bronchitis	C	?	134/?6 (104)	128	11 28	14 4	?2	0 81
20	1 5?		? hr	?9	121/69 (93)	112	11 95	13 4	75	0 81
J S	W M	Post gastrect my	C	50	139/79 (104)	93	9 82	9 1	71	1 1?
3?	? 14		2 hr	61	75/?1 (66)	74	9 46	7 0	?8	0 89
G I	N M	Mediastinal tumor	C	86	130/88 (104)	95	13 86	13 2	69	1 09
48	1 95		2 hr	96	131/93 (108)	71	15 06	10 7	73	1 5?
O C	N F	Diastolic hyperten sion no cardio megaly	C	?9	173/105 (135)	127	13 41	17 0	?8	1 06
3?	1 80		? hr	87	161/99 (1?2)	113	1? 0?	13 ?	71	1 08
O S	N M	Lende abscess	C	?0	101/66 (83)	118	10 33	12 2	64	0 ?0
30	1 67		2 hr	?9	99/63 (80)	110	10 57	11 6	?1	0 73
J Z	W M	Alcoholic gastritis	C	80	139/?8 (10?)	10?	13 45	13 7	68	1 00
41	1 71		2 hr	88	104/?4 (87)	82	12 36	10 1	64	1 06

Ini l det rm nat n (C) t e ned t 3 F and 40 per ce t h m d ty Experim ntal d term at on (h) fte 2 h ur po u to 95°F a d 40 per nt umid ty F b y t al br i t n ef ote t T bl I

Table III Individual determinations for 8 subjects with enlarged left ventricles and normal wedge pressures (procedure as for subjects in Table II)

Patient Age (yr)	Race Sex B S	Diagnosis		Heart rate	PBA	CBF	AVD	VMRO	c_c EVT	CVR
A F	N M	HCVD	C	64	192/112 (140)	118	11 60	13 7	67	1 18
38	1 74		2 hr	79	170/104 (125)	92	10 50	9 7	74	1 36
A W	N F	HCVD	C	60	220/113 (166)	95	12 13	10 3	78	1 95
43	1 60		2 hr	71	178/96 (133)	78	12 33	9 6	81	1 71
S M	N M	HCVD	C	66	166/108 (131)	143	9 37	13 3	54	0 97
43	1 95		2 hr	75	140/92 (112)	109	[illegible] 29	10 1	52	1 03
M C	N F	Idiopathic enlargement of left ventricle	C	77	122/77 (97)	105	13 56	14 2	78	0 97
52	1 75		2 hr	84	113/70 (88)	92	12 57	11 5	71	[illegible] 96
R C	W M	RHD AS MI	C	76	146/78 (102)	131	11 94	15 6	65	0 78
47	1 87		2 hr	88	135/70 (90)	123	11 34	13 9	65	0 73
P Q	N F	RHD MI	C	75	156/88 (114)	114	11 20	12 8	72	[illegible] 96
41	1 67		2 hr	69	130/80 (94)	90	11 74	10 1	69	1 04
O D	N M	HCVD	C	62	1[illegible]0/104 (132)	98	11 60	11 3	73	1 35
51	1 80		2 hr	60	160/96 (123)	80	11 47	9 2	[illegible]4	1 54
M B	W F	HCVD	C	76	218/124 (164)	99	11 13	11 0	66	1 66
35	1 43		2 hr	85	186/107 (136)	94	10 98	10 3	66	1 44

HCVD Hypertensive cardiovascular disease *RHD* Rheumatic heart disease AS Aortic stenosis *MI* Mitral insufficiency For key to other abbreviations, see footnote to Table I

Table IV Individual determinations for subjects with enlarged left ventricles and elevated wedge pressures (procedures as for subjects in Tables II and III)

Patient Age (yr)	Race Sex B S	Diagnosis		Heart rate	PBA	CBF	AVD	VMRO	c EVT	CVR
M B	W M	ASHD	C	[illegible]4	146/92 (108)	98	14 10	13 8	69	1 10
42	1 87		2 hr	[illegible]9	130/84 (94)	[illegible]2	14 47	10 4	71	1 30
A C	N F	HCVD	C	64	240/118 (168)	104	14 35	14 9	80	1 62
54	1 80		2 hr	68	169/91 (119)	85	11 35	9 7	68	1 40
F T	N M	HCVD	C	60	199/127 (153)	116	12 39	14 4	74	1 37
45	2 08		2 hr	79	144/104 (121)	118	11 70	13 8	74	1 07
L B	N F	HCVD Remote myocardial infarction	C	[illegible]5	174/[illegible]0 (135)	83	14 91	12 4	81	1 63
58	1 60		2 hr	78	157/101 (124)	69	13 67	9 4	81	1 80
H P	W F	RHD MI	C	74	136/88 (98)	87	13 80	11 3	66	1 19
39	1 65		2 hr	80	122/80 (81)	64	14 10	9 0	68	1 26
C P	N F	HCVD	C	60	225/120 (168)	162	13 28	21 5	76	1 04
35	1 [illegible]8		2 hr	71	165/100 (125)	106	12 07	12 8	75	1 18
P A	W F	ASHD	C	105	142/92 (113)	105	12 72	13 4	71	1 08
43	1 59		2 hr	115	137/86 (107)	109	11 96	13 0	66	0 98
D P	N M	HCVD	C	84	201/92 (134)	129	8 9[illegible]	11 6	72	1 04
64	1 65		2 hr	97	173/84 (115)	128	8 77	11 2	78	0 90

ASHD Arteriosclerotic heart disease *HCVD* Hypertensive cardiovascular disease *RHD* Rheumatic heart disease *MI* Mitral insufficiency For key to other abbreviations, see footnote to Table I

Table V. Averages, percentile changes, and significance analyses for the four groups

	Heart rate		LBI		CBF		LLD		LVEO		LVT		CTR	
A. Control														
C	6		103		121		10 73		11 5		67		1 06	
2 hr	71	+ 6 4	121	+11 0	121	0	10 91	+1 4	11 0	+13 0	68	+1 5	1 16	+9 4
P (C vs 2)	< 1 > 05		< 01 > 005				< 3 > 2		< 3 > 2		< 3 < 1		> 3 > 2	
B. Normal heart, heat														
C	74		104		112		12 12		14 7		70		0 95	
2 hr	82	+10 8	91	−12 5	96	−14 3	11 73	−3 2	11 2	−18 2	67	−4 3	0 99	+4 2
P (C vs 2)	< 001		< 02 > 01		< 001		< 3 > 2		< 001		< 3 < 2		< 6 > 5	
C. Enlarged left ventricle, normal wedge pressure, heat														
C	71		130		112		11 56		12 8		60		1 21	
2 hr	79	+11 3	113	−13 1	95	−15 2	11 21	−3 0	10 5	−17 9	60	0	1 33	+0 7
P (C vs 2)	< 001		< 001		< 001		< 1 > 05		< 001				< 7 > 6	
D. Enlarged left ventricle, elevated wedge pressure, heat														
C	74		135		110		13 06		14 2		44		1 25	
2 hr	83	+12 2	111	−16 9	94	−14 5	12 25	−6 2	11 2	−21 1	43	−1 3	1 23	−0 3
P (C vs 2)	< 005 > 001		< 005 > 001		< 05 > 02		< 1 > 05		< 02 > 01		< 9		< 9	

*Significance analyses of Control Group A versus Groups B, C, and D**

	Heart rate	LBI	CBF	LLD	LVEO	LVT	CTR
p (Controls vs B)	< 005 > 01	< 01 > 005	< 3 > 2	< 5 > 4	< 05 > 02	—	< 8 > 7
p (Controls vs C)	> 001	> 001	< 005 > 001	< 4 > 3	< 05 > 02	—	< 4 > 3
p (Controls vs D)	< 01 > 005	< 005 > 001	< 4 > 3	< 2 > 1	< 05 > 02	—	< 5 > 4

*The comparison ... between the final percentile change in Group A ... the other groups (F ... than 30) For key to abbreviations ... Table 1

tients under mild oral sedation (Pentobarbital sodium 0.1 Gm.) after they had fasted overnight. After determination of the central venous pressures, entry of a No. 7F bird's eye catheter into the coronary sinus via a left antecubital vein cutdown, and introduction of an intra-arterial needle into the ipsilateral brachial artery, the subjects were allowed to rest quietly for 20 minutes. The initial flows in the comfortable environment were then obtained. The patients in Groups B, C, and D were then placed in a constant temperature room pre-heated to 98 F. with 40 per cent relative humidity and were covered only by suitable small towels. The experimental data were obtained after 2 hours and the study was terminated.

The technique employed for the determination of coronary (left ventricular) blood flow (CBF) was the nitrous-oxide saturation desaturation method of Goodale and Hackel,[4] wherein the flow is expressed as milliliters per 100 Gm. of left ventricle per minute. Nitrous oxide tensions were manometrically determined on the Van Slyke apparatus. Samples of blood from the coronary sinus and brachial artery were analyzed spectrophotometrically for oxygen by the method of Hickam and Frayser,[5] and for glucose,[7] lactate,[1] and pyruvate.[8]

Intra-arterial pressures were transduced via a Statham strain gauge and suitably inscribed on a Sanborn or Brush direct-writing recorder. Left ventricular oxygen uptake ($VMRO_2$), per cent of myocardial oxygen extraction, and coronary vascular resistance (CVR) were calculated by the appropriate formulas.[4]

Results

The data for the individual groups are presented in Tables I, II, III, and IV, respectively. Averages, percentile changes, and statistical analyses (Fisher's "t" test, groups less than 30) are presented in Table V.

The control subjects (Group A) exhibited no significant changes in heart rate, CBF, brachial artery—coronary sinus arteriovenous oxygen difference (AVD), VMRO, per cent oxygen extraction, and CVR. Mean brachial arterial pressure rose significantly, perhaps a manifestation of some apprehension as the test progressed.

In the other groups which were exposed to the warm and dry environment, there were significant increases in the heart rate and decreases in the mean brachial arterial pressure, CBF, and $VMRO_2$. These changes were also significant when compared to the findings in the control group except for the CBF in Groups B and D. AVD, per cent myocardial oxygen extraction, and CVR demonstrated no significant changes.

Glucose, lactate, and pyruvate arteriovenous differences were within normal limits during the initial determinations and showed no significant changes after the 2 hour period in any group. The detailed data are not reported.

Discussion

In a previously reported study[8] involving patients with enlarged left ventricles who were exposed for 2 hours to an environment of 98 F. and 40 per cent relative humidity, the grossly calculated left ventricular work (cardiac output × mean brachial arterial pressure) decreased significantly. This was due to the fact that the cardiac output remained unaltered while the brachial arterial pressure consistently decreased. Since the effect was achieved with no pharmacologic manipulations, it was thought that a physiologic reduction in the blood pressure brought about by a warm and dry environment might actually be beneficial to an "overworked" left ventricle, at least on a short-term basis.

The present experiments extend the previous findings. The two parameters which showed significant and consistent changes in all 3 experimental groups individually, as well as when compared to the findings in the control subjects, were the brachial arterial pressure and the left ventricular myocardial oxygen consumption. Both decreased significantly, and a fairly significant positive correlation was demonstrated between the reduction in the arterial pressure and the fall in left ventricular oxygen consumption ($r = 0.455$, $p = < 0.05 > 0.02$). The reduced oxygen consumption is an expression of the decreased metabolic demand for oxygen by the left ventricle under a simple physiologic

cumstance which reduces the work load The reduction in CBF may be attributed to a combination of a decrease in the perfusion pressure and a reduction in myocardial oxygen demand with no evidence for the development of a block mechanism thus this reduction may be considered to be a benign one

The findings are in contrast to the increase in the cardiac work load which occurs in individuals exposed for short periods to a hot and humid environment and suggest that in quiet resting man a warm and dry environment may have a salutary effect

Summary

Subjects with normal hearts as well as patients with enlarged left ventricles compensated or in left ventricular failure were exposed for 2 hours to a dry warm environment of 98 F and 40 per cent relative humidity

Brachial arterial pressure and left ventricular myocardial oxygen consumption decreased significantly There was a positive correlation between these measurements

These changes are not harmful to the overburdened left ventricle and within the design of the experiment may actually be considered to be beneficial in the case of resting subjects

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Vectorcardiographic and electrocardiographic findings in myotonia atrophica

A study employing the Frank lead system

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Since Griffith[1] observed marked bradycardia and irregular cardiac action in a patient with classic myotonia atrophica the concept has been entertained that the cardiovascular system might be involved in this disease Maas[2] in 1920 found a prolonged P R interval in a patient studied electrocardiographically and since then many others have shown the prevalence of electrocardiographic changes A compendium of the larger series reported[3-5] revealed that of 195 patients 113 had abnormal electrocardiograms (58 per cent) Minor conduction disorders were common as was left axis deviation[5] and it was unusual to note more serious findings Clinical indications of heart disease were exceptional and it was thought that the heart probably did not play a major role in the over all picture of this disorder

The purpose of this paper is to report on and compare the vectorcardiographic and electrocardiographic findings in a series of patients with myotonia atrophica emphasizing the frequency of myocardial involvement as demonstrated by the vectorcardiogram It is believed that these findings may have some significance in relation to the course and the cause of death in this disease

Materials and methods

Seventeen patients (12 males and 5 females) with classic myotonia atrophica[6] who had previously been evaluated by the medical and neurological services of the North Carolina Memorial Hospital were available for study Their age range was 24 to 60 years and the duration of symptoms ranged from 3 to 30 years None had cardiovascular symptoms and only one patient (Patient 12) had any abnormal cardiovascular findings on physical examination Eight of the 17 patients had a family history of the classic disease The patients were studied by radiologic examination of the chest 14 lead electrocardiograms and spatial vectorcardiograms None of the patients was taking procaine amide quinine or quinidine or any drug which might affect myocardial conduction *Table I* summarizes the findings

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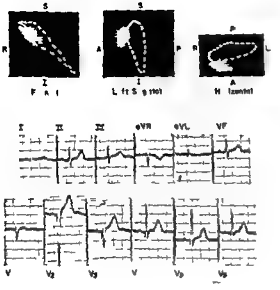

Fig. 1. Patient S. S. *Vectorcardiograms show:* Loss of anterior instantaneous vectors in the left sagittal and horizontal planes. These changes are consistent with infarction in the anterior area. *Electrocardiogram shows:* Prolongation of Q-T interval and deep Q waves in Leads aVL, V-V, consistent with anteroseptal myocardial infarction.

The vectorcardiograms were made from a Sanborn 350M vectorcardiographic unit using the Frank lead system.[18] The loops (frontal, left sagittal, and horizontal) were photographed directly from the oscilloscope with a 110B Polaroid Land camera equipped with copying lens. The timing interrupter was set for 2.5 milliseconds with the head of the comet designating the direction. The gain on the amplifier units was frequently increased to either 2X or 5X normal gain to evaluate more clearly the initial instantaneous vectors (0 to 0.015 sec.). Measurements were made from the vectorcardiograms for initial, maximal, and terminal angles (QRS) as well as for mean initial vectors, instantaneous 0.02 sec. vectors, maximal vectors, and mean terminal vectors.

For the purposes of this paper, the mean initial vector consists of the instantaneous vectors which occur between the zero point and the first significant change in direction of the loop. The instantaneous 0.02 sec. vector is that vector which occurs at 0.02 sec. from the zero point. The maximal vector is that instantaneous vector which has the greatest magnitude from the zero point. The mean terminal vector is composed of the instantaneous vectors which occur between the last major change in direction of the loop and the zero point. In general, the mean initial vector, maximal vector, and mean terminal vector correspond to the instantaneous vectors which occur at the QRS angles of McCall and associates.[3]

Vectorcardiograms were also made concurrently on 27 individuals who were free from cardiovascular disease by the usual clinical criteria. The group consisted of medical students, house officers, and technicians whose ages ranged from 18 to 40 years. The findings in the 27 normal vectorcardiograms are presented in Table II.

Results

Radiography. Radiologic studies of the chest disclosed clear lung fields and a normal configuration and size of the heart in 14 patients. The other 3 were found to have moderate cardiomegaly. Of these, one patient had left atrial enlargement, one had left ventricular predominance,

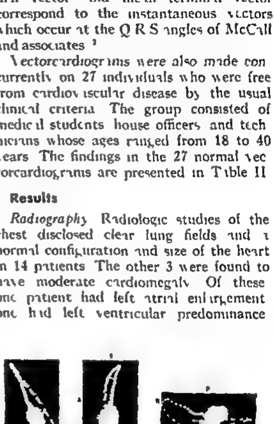

Fig. 2. Patient K.S. *Vectorcardiograms show:* Loss of diaphragmatic instantaneous vectors in the frontal plane and left sagittal plane, and loss of posterior instantaneous vectors in the left sagittal and horizontal planes. These changes are consistent with infarction in the posterior-diaphragmatic area. *Electrocardiogram shows:* Left axis deviation, prolongation of QRS interval to 0.10 sec. The initial 0.04-sec. vector is normally directed with marked left axis deviation of the terminal 0.04 sec. vector. The changes are consistent with left ventricular parietal block.

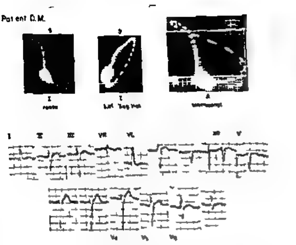

Fig. 3. Patient D. M. *Vectorcardiograms show*: Initial instantaneous vectors (0.01 to 0.03 sec.) normally directed with the mean terminal vector directed to the left, superiorly, and posteriorly. These changes are consistent with left ventricular parietal block. *Electrocardiogram shows*: P-R interval of 0.22 sec., QRS interval of 0.10 sec., left axis deviation. In addition, the initial 0.04 QRS vector is normally directed with marked left axis deviation of the terminal 0.04 sec. QRS vector. These changes represent left ventricular parietal block.

and the third patient had generalized enlargement of the heart. In addition to cardiomegaly, one patient had emphysema, kyphosis, and calcification of the aortic knob. It is of interest that 3 patients had elevation of the right hemidiaphragm, a finding previously reported by Caughey and Gray.[14]

Electrocardiography. Twelve of the 17 patients had abnormal tracings and these are tabulated in Table III. Seven had a relatively slow sinus rate of 60 per minute and disturbance of cardiac rhythm consisting of atrial flutter was found in 2 instances. Conduction disturbances were most frequent and included (1) prolongation of P-R interval (greater than 0.20 sec.), (2) prolongation of QRS interval (greater than 0.09 sec.), and (3) prolongation of the Q-T interval corrected for heart rate. Elevation of the S-T segment (maximum of 3 mm.) was found in 4 cases and occurred usually in Leads I, II, V_5, and V_6, but in one case the elevation occurred in Leads V_3 and V_4. T wave changes were found in 3 instances; these consisted of T wave flattening in 2 patients and in the third, deep T wave inversion in Leads III and aV_F and all precordial leads. One tracing revealed prominent U waves. Left axis deviation was found in 5 cases and abnormal transition zones were present in 3 cases (counterclockwise rotation in 2 and clockwise rotation in one). Two tracings were consistent with anterior myocardial infarction, manifested in one by deep Q waves in Leads aV_L, V_1, and V_2 and in the other by the lack of development of R waves in the medial precordial leads. An additional electrocardiogram revealed small R waves in the medial precordial leads but the significance of this finding was undetermined. Left ventricular parietal block[15-17] was diagnosed in 3 cases on the basis of a normal or semihorizontal mean vector for the first 0.04 sec. of the QRS complex with left axis deviation of the mean vector for the terminal 0.04 sec. of the QRS complex. One tracing was consistent with either incomplete right bundle branch block[18]—as manifested by prominent S waves in the limb leads and r-r' configuration in the right-sided precordial leads—or an $S_1S_2S_3$ syndrome.[19] Three of the 7 instances of intraventricular conduction defect (QRS interval greater than

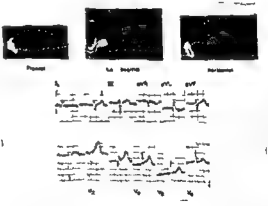

Fig. 4. Patient D. G. *Vectorcardiograms show*: Loss of diaphragmatic instantaneous vectors in the frontal and left saggital planes and the loss of anterior instantaneous vectors in the left saggital and horizontal planes. These changes are consistent with infarction in the antero-diaphragmatic area. *Electrocardiograms shows*: Sinus rhythm of 60 per minute, P-R interval of 0.28 sec., QRS interval of 0.12 sec., left axis deviation, S-T segment elevation in Leads V_2, V_3, V_4, and a Q wave in Leads V_2 and V_3, consistent with anterior myocardial infarction.

0.09 sec.) were thought to be due to left ventricular parietal block. 2 occurred in the tracings consistent with myocardial infarction, and 2 remained unexplained. Thus a total of 12 types of electrocardiographic abnormalities was found and these results are consistent with those previously reported.[3,14] Figs. 1 to 6 illustrate some of the electrocardiographic abnormalities.

Vectorcardiography. The findings in our 27 normal vectorcardiograms are presented in Table II and are consistent with those reported in the literature.[illegible, 3] The slightly more posterior angle in the horizontal plane in our normal cases is probably due to placement of the electrodes at points A and C in the Frank system. Our normal values will not be discussed further but are presented to validate the method and to add 27 normal cases to the literature on the Frank system.

The vectorcardiographic findings in the 17 patients with myotonia atrophica fall

Table I

	Patient Age (yr.) Race Sex	Duration of myotonia atrophica	Family history	Cardiovascular respiratory symptoms	Cardiovascular clinical findings
1	E. S. 37 W M	20 yr.	Present	None	None
2	K. S. 56 W M	30 yr.	Absent	None	None
3	L. F. 48 W M	18 yr.	Absent	None	None
4	G. B. 39 W M	8 yr.	Absent	None	None
5	E. P. (M.) 60 W F	Since childhood	Absent	None	None
6	O. H. 45 W F	12 yr.	Absent	Leg swelling (nonspecific)	None
7	L. D. 38 W M	10 yr.	Absent	None	Grade 2 systolic murmur at left sternal border
8	V. H. 47 W M	17 yr.	Absent	None	None
9	M. J. 46 W F	20 yr.	Absent	None	None
10	M. V. 49 W M	10 yr.	Present	None	None
11	V. F. 54 W F	10 yr.	Present	None	None
12	M. C. 42 W F	All life	Present	None	Atrial flutter in 1958
13	Laf. L. 40 W M	11 yr.	Absent	None	None
14	G. T. 24 N M	3 yr.	Absent	None	Apex beat outside midclavicular line
15	D. C. 54 N M	28 yr.	Present	None (rheumatic fever)	Clinical mitral regurgitation
16	D. M. 56 W M	13 yr.	Absent	Dyspnea secondary to lung trouble	None
17	F. F. [illegible] W M	5 yr.	Absent	None	None

into four distinct groups *Group I* consists of 3 patients whose values (configuration angles voltage timing direction) fall within the limits of normal *Group II* consists of 4 patients whose vectorcardiographic loops are thought to represent the $S_1S_2S_3$ syndrome The mean initial vectors and instantaneous 0 02 sec vectors are normally directed in all three planes—but the mean terminal vectors (0 042 to 0 065 sec) are directed to the right superiorly and posteriorly in the frontal left sagittal and horizontal planes respectively The values for this group are shown in Table IV and Fig [illegible] shows a characteristic $S_1S_2S_3$ loop *Group III* consists of 6 patients whose vectorcardiograms show a displacement of the instantaneous vectors which simulates exactly the displacement seen in infarction of the myocardium Three of the 6 patients in this group had lost all of the initial vectors in the left sagittal and horizontal planes The fourth and fifth patients not only had

X ray findings	*Electrocardiographic findings*	*Vectorcardiographic findings*
Normal	Anteroseptal myocardial infarction prolonged Q T interval	Infarction
Normal (slight elevation of right hemidiaphragm)	Left ventricular parietal block left axis deviation generalized T wave flattening QRS = 0 10 sec	Infarction
Normal	S-T segment elevation in II III V_3 and V_4 VSR = 60	$S_1 S_2 S_3$
Normal	Probably within normal limits slight counterclockwise rotation VSR = 60	$S_1 S_2 S_3$
Emphysema left ventricular hypertrophy kyphosis elevation of right hemidiaphragm calcification of aortic knob	Q wave in I aV$_L$ interventricular conduction defect T wave inversion in III aV$_F$ and all precordial lead Q T interval prolonged VSR = 60	Left ventricular parietal block
Normal	Left ventricular parietal block left axis deviation Q T interval prolonged QRS = [illegible] 10 sec VSR = 60	Infarction
Normal	Prolonged Q-T interval probably within normal limit U waves	Normal
Normal	Probably within normal limits	Normal
Normal	Atrial flutter left axis deviation counterclockwise rotation	Left ventricular parietal block
Normal	Probably within normal limits (with slight elevation of S-T segments in V and V)	Normal
Normal	First-degree heart block Q T interval prolonged counterclockwise rotation	Infarction
Normal	First-degree heart block generalized T wave flattening VSR = 60	Infarction
Normal	First degree heart block S-T segment elevation in I V_4	Left ventricular parietal block
Slight left ventricular hypertrophy elevation of right hemidiaphragm	*$S_1 S_2 S_3$ or incomplete right bundle branch block*	$S_1 S_2 S_3$
Moderate enlargement	First-degree heart block interventricular conduction defect left axis deviation Q wave *in* aV$_L$ V_2 V_3 consistent with antero myocardial infarction S-T segment elevation in V_3 QRS = 0 12 sec. VSR = 60	Infarction
Normal	First-degree heart block left ventricular parietal block left axis deviation clockwise rotation small R waves in mid precordial lead QRS = 0 10 sec	Left ventricular parietal block
Normal	Within normal limits	$S_1 S_2 S_3$

lost the initial anterior instantaneous vectors in the left sagittal and horizontal planes but in addition the frontal and left sagittal planes revealed loss of diaphragmatic instantaneous vectors. The sixth patient revealed loss of anterior diaphragmatic and posterior instantaneous vectors in the three planes. Two patients in this group have loops prolonged to 0.12 sec. Figs. 1, 2, and 4 illustrate the characteristic loss of instantaneous vectors. *Group II* consists of 4 patients whose vectorcardiographic loops reveal the instantaneous 0.02 sec. vector to be between +45° and +75°, the maximal vector (0.0325 sec. to 0.04 sec.) to be between +10° and +35°, and the mean terminal vector (0.045 sec. to 0.065 sec.) to fall between −53 and −158° in the frontal plane. The left sagittal plane in this group reveals the mean initial vector and instantaneous 0.02 sec. vector to be directed between +121° and +151°. The maximal and mean terminal vectors (0.04 to 0.065 sec.) are identical and are directed posteriorly and superiorly. The horizontal plane reveals that the mean initial vectors (0.01 to 0.02 sec.) range between +40 and +60°. The mean terminal vectors are directed to the left and posteriorly (−50° to −117°). It is thought that this group represents a form of left ventricular parietal block, with the mean initial vectors and the instantaneous 0.02 sec. vectors essentially normally directed and the mean terminal vectors (0.045 to 0.065 sec.) deviated to the left, superiorly, and posteriorly. The duration of the loops is normal in 2 cases (less than 0.09 sec.) and in the other 2 cases it is prolonged (greater than 0.09 sec.). Figs. 3 and 5 and Table IV, respectively, illustrate and detail the findings.

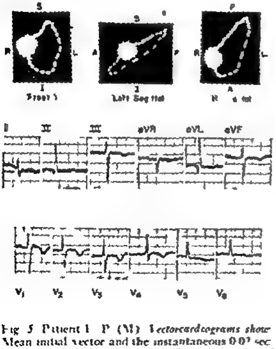

Fig. 5. Patient 1. P. (M.). *Vectorcardiograms show:* Mean initial vector and the instantaneous 0.02 sec. vector normally directed, with the mean terminal vector directed to the left, superiorly and posteriorly. These changes are consistent with left ventricular parietal block. *Electrocardiogram shows:* Sinus rate of 60 per minute, QRS interval of 0.10 sec., Q-T interval of 0.48 sec., horizontal axis, T wave inversion in Lead III, aVF, and all precordial leads, and a Q in Leads I and aVL.

Discussion

The vectorcardiogram was found to reflect abnormalities of the myocardial activation process more accurately than did the electrocardiogram. The electrocardiogram, however, was found to be superior in detecting time-related abnormalities such as rate, rhythm, and conduction intervals.

Five of our 17 patients (29 per cent) had

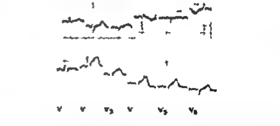

Fig. 6. Patient J. P. *Vectorcardiograms show:* Initial instantaneous vectors (0.01, 0.02, and 0.03 sec.) normally directed, with the mean terminal vectors directed to the right, superiorly, and posteriorly. These changes represent the $S_1S_2S_3$ type of loop. *Electrocardiogram shows:* A semivertical axis. It is thought to be within normal limits.

Table II. Vectorcardiographic findings in study of normal subjects

Type	*Qualifications*	*Range*	*Mean*	*± 2 S D*
Frontal plane				
A Mean initial vector	1 Angle	−90° to −149	−105	± 44
	2 Voltage (mv)	135 to 260	202	
	3 Time (sec)	0075 to 0100	00875	
B Instantaneous 0 07 sec vector		+17 to +47°	+32 9°	± 15 57
C Maximal instantaneous vector	1 Angle	+20° to +60°	+38 8°	± 22
	2 Voltage (mv)	878 to 2 16	1 46	
	3 Time (sec)	020 to 0475	0748	
D Mean terminal vector	1 Angle	+114 to −115	−160°	Wide scatter
	2 Voltage (mv)	250 to 107	405	
	3 Time (sec)	0350 to 0725	0502	
Left sagittal plane				
A Mean initial vector	1 Angle	a +180° to −125	a −156	± 37
		b +139° to +180°	b +157 8°	± 28
	2 Voltage (mv)	05 to 878	276	
	3 Time (sec)	005 to 020	011	
B Instantaneous 0 07 sec vector		+115 to −174	+142	± 36
C Maximal instantaneous vector	1 Angle	a +10° to +53	+34 a + b =	± 32
		b +55 to +110°	+82 +69°	± 27
	2 Voltage (mv)	335 to 2 03	1 14	
	3 Time (sec)	025 to 050	0374	
D Mean terminal vector(s)	1 Angle	−9° to −43	−17 5	Wide scatter
	2 Voltage (mv)	413 to 1 15	77	
	3 Time (sec)	045 to 060	054	
Horizontal plane				
A Mean initial vector (Q)	1 Angle	+80° to +146	+110 4	± 30
	2 Voltage (mv)	09 to 866	233	
	3 Time (sec)	0025 to 015	0101	
B Instantaneous 0 07 sec vector		a +20° to +96	+41 8	± 41
		b −39° to −10°	−21 2	± 26
C Maximal instantaneous vector	1 Angle	a +15 to −70°	+4 5	± [illegible]
		b −21 to −53	−36	± [illegible]
			a + b = −13	
	2 Voltage (mv)	[illegible] to 1 54	1 23	
	3 Time (sec)	020 to 045	035	
D Mean terminal vector	1 Angle	−90° to −145	−117 [illegible]	± [illegible]
	2 Voltage (mv)	2 0 to 1 25	772	
	3 Time (sec)	040 to 065	053	

left axis deviation by electrocardiogram. These patients with left axis deviation were found on vectorcardiographic study to be among the groups with either infarction or left ventricular parietal block. Changes consistent with myocardial damage were revealed in 10 of our 17 patients (60 per cent) by vectorcardiographic findings of either displacement of instantaneous vectors or ventricular parietal block. These observations tend to support the clinical hypothesis that suggests the presence of involvement of the myocardium similar to the involvement of skeletal muscle in myotonia atrophica. In a review of the American and British medical literature we were able to find 17 autopsied cases of myotonia atrophica, of which 9 cases showed myocardial involvement.[4, 5, 10, 14-20] The myocardial involvement consisted of fatty infiltration, areas of myocardial fibrosis, and abnormal pseudo hypertrophy of the muscle fibers.

The displacement of instantaneous vectors on the vectorcardiograms in Group III is identical to that seen in myocardial in-

Table III Electrocardiographic findings

Classification	Frequency of occurrence
A Normal	5 (29%)
B Abnormal	12 (7 %)
1 Atrial flutter	2 (1 18%)
2 Prolonged P R interval (greater than 0.20 sec)	5 (29.5%)
3 Prolonged QRS interval (greater than 0.08 sec)	7 (41%)
4 Prolonged Q T interval	6 (35%)
5 Left axis deviation	5 (29.5%)
6 S-T segment elevation	4 (23.5%)
7 T wave flattening or inversion	3 (17.5)
8 Infarction	2 (12%)
9 Left ventricular parietal block	3 (17.5%)
10 Incomplete right bundle branch block or $S_1S_2S_3$	1 (0.59%)
11 U waves	1 (0.59%)
12 Small R waves in medial precordial lead	1 (0.59%)

The percentage values for subgroups under Group B represent the percentage of occurrence of each abnormality in the total number of patients studied. Many patients exhibited more than one abnormality.

farction but it should be re-emphasized that none of our patients had clinical histories suggestive of coronary artery disease with infarction.

From the pathologic descriptions of the myocardium in myotonia atrophica it would appear that this disease represents another process by which vectorcardiographic changes consistent with myocardial infarction are produced without frank tissue necrosis.

The $S_1S_2S_3$ loops may represent a variant of the normal or a form of myocardial involvement which as of this time is unexplained. This type of loop may occur in healthy young normal individuals and also in persons suspected of having posterior myocardial infarctions. It has also been seen in congenital heart disease and cor pulmonale.[10] In this study the $S_1S_2S_3$ loop was present in the younger patients with shorter duration of myotonia atrophica.

Since our series involved a small group of patients conclusions which involve the age of patients and duration of illness compared with the degree of electrocardiographic and vectorcardiographic abnormalities would probably be invalid. In general however it appears that the younger patients with shorter duration of disease have fewer cardiac abnormalities.

The abnormalities derived from the vectorcardiograms in this study are clearly more striking than those demonstrated by the electrocardiogram more than half the patients had evidence of significant myocardial involvement. Left axis deviation a common electrocardiographic finding in patients with myotonia atrophica must be considered more in terms of peri-infarction block or left ventricular parietal block for there is certainly little evidence that left ventricular hypertrophy is always responsible. Thus it is possible that cardiomyopathy may play a more significant part in this disease than has hitherto been realized. The cause of death in myotonia atrophica is not well documented but it is our impression that sudden death is not uncommon and it may be speculated that such deaths could be due to cardiovascular causes. Autopsy reports are infrequent with an incomplete study of the heart nevertheless as previously noted cardiac involvement has been documented in over half the autopsy cases. A further study of this aspect of the disease is needed in order to establish the significance of our vectorcardiographic findings.

Summary

1 Seventeen patients with classic myotonia atrophica as manifested by clinical findings and electromyographic studies were investigated by chest x-ray film electrocardiogram and spatial vectorcardiogram employing the Frank lead system

Table IV

Frontal					
Classification	*Instantaneous 0.02 sec vector*	*Instantaneous maximal vector*		*Mean terminal vector*	
		Angle	*Time*	*Angle*	*Time*
$S_1S_2S_3$ (4 patients)	+23 to +57	+70° to +65	0 025 to 0 035	−135 to +106	0 0425 to 0 0400
LVPB† (4 patients)	+45 to +75	+10° to +35	0325 to 0400	−53 to −158°	0 045 to 0 065

Left Sagittal							
Classification	*Instantaneous 0 02 sec vector*	*Mean initial vector*		*Instantaneous maximal vector*		*Mean terminal vector*	
		Angle	*Time*	*Angle*	*Time*	*Angle*	*Time*
$S_1S_2S_3$ (4 patients)	+145 to +140°	−123 to −150°	0 01	+74 to +157°	0 025 to 0 040	−30° to +45	0 0425 to 0 0675
LVPB† (4 patients)	+ 21 to +151						

Horizontal							
$S_1S_2S_3$ (4 patients)	+45 to +65			0 to +50°	0 025 to 035	−105 to −1[illegible]	0 045 to 0 060
LVPB† (4 patients)	+40° to +60°	+73 to +115	0 01 to 0 02	−50 to +35	0 035	−30° to −11°	0 05 to 0 0575

In 3 out of 4 patients the maximal instantaneous and mean terminal vectors are essentially the same. The fourth patient had [illegible] configuration [illegible] the mean terminal vector exceeded in magnitude what would ordinarily be the maximal [illegible] vector.
†Left ventricular parietal block.

Twenty seven normal individuals were studied with the Frank system and are reported on to validate our method and to add to the normal findings in the literature

2 In 12 (71 per cent) of the 17 patients there was a total of 12 different abnormal electrocardiographic findings These consisted primarily of conduction defects (P R interval greater than 0 20 sec 29 5 per cent QRS interval greater than 0 09 sec 41 per cent Q T interval in excess for rate 35 per cent) Five patients (29 5 per cent) were found to have left axis deviation S-T segment elevation was present in 4 patients (23 5 per cent) Three patients (17 5 per cent) were thought to have a form of left ventricular parietal block The other major abnormalities included T wave changes (17 5 per cent) and changes consistent with myocardial infarction (12 per cent) Seven patients (41 per cent) had a sinus rhythm of 60 per minute

3 Spatial vectorcardiography revealed 3 patients with normal loops (17 6 per cent) 4 patients with $S_1S_2S_3$ loops (23 5 per cent) 4 with left ventricular parietal block (23 5 per cent) [illegible]

ment of instantaneous vectors in anterior diaphragmatic or posterior areas identical to that seen in myocardial infarction (35.4 per cent). The cause of left axis deviation in the electrocardiogram of 5 of our patients was either "infarction" or left ventricular parietal block by vectorcardiographic findings. The findings of "infarction" and left ventricular parietal block in 10 patients (60 per cent) would imply involvement of myocardial tissue. Prolongation of the QRS interval in the electrocardiogram (greater than 0.09 sec.) and vectorcardiogram in this study was due to either "infarction" or left ventricular parietal block. The vectorcardiogram proved to be superior to the standard 14 lead electrocardiogram in the detection of abnormalities of the ventricular activation process. The electrocardiogram was the better measurement of P-R and Q-T intervals, rate, rhythm, and S-T segment and T wave changes.

4. The findings of conduction defects in the electrocardiogram and of significant changes in the ventricular activation process in 60 per cent of patients in the vectorcardiogram would seem to be consistent with the reported autopsy findings of myocardial involvement.

5. The findings of "infarction" in the absence of clinical history would imply that cardiac involvement in myotonia atrophica brings about another "infarction" pattern *without* true coronary artery disease with myocardial infarction.

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Detection of intracardiac shunts with the platinum electrode, using a simplified percutaneous approach

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Many attempts have been made to devise a rapid technique for screening patients suspected of having a left-to-right intracardiac shunt. Precordial scanning after the intravenous injection of a radioisotope has been the most widely used approach to this problem. This technique is effective in demonstrating the presence of a moderate to large shunt, although the results may be equivocal in the presence of small intracardiac shunts.[1] Recent work has suggested that pulmonary vascular dilution curves recorded with an external detector may be more sensitive than precordial curves. However, the equipment required for performing these procedures is not readily available in most outpatient departments.

The need for such special techniques is infrequent when evaluating the patient with a left-to-right shunt of moderate size. However, the presence of a small left-to-right shunt may be less readily appreciated during clinical evaluation. Thus the desirability of a simple technique for rapid determination of the presence of a small left-to-right shunt is apparent.

The usefulness of the highly sensitive hydrogen-platinum electrode system[3,4] during routine cardiac catheterization for the detection of the small intracardiac shunt has been reported.[5,6] Recent work with a Teflon-insulated stainless steel wire with a platinum electrode on one end demonstrated that this small electrode could be easily passed in a retrograde fashion into the heart without fluoroscopy,[7] although the wire may be visualized with an image intensifier if desired. The usefulness of this technique as a simple bedside diagnostic maneuver in the identification of complex arrhythmias has been evaluated.[8] Because of the ease with which the electrode can be passed into the heart, it seemed feasible to use it for the purpose of detecting shunts, using hydrogen as the indicator.

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This paper reports the usefulness of this technique for the detection of left to right shunts.

Methods

The wire employed in these studies is highly flexible stainless steel size O and coated with Teflon except for the ends.* A piece of platinum 125 inches by 032 inches is attached to one end and the other end is left bare for connecting to an external lead. A small alligator clamp is soldered to the bare end to facilitate attachment to the external lead.

A median arm vein is selected which will accept an 18 gauge thin walled needle and the area is cleansed and draped. Under sterile conditions the needle is positioned within the vein and the platinum tipped end of the wire is advanced through the needle for a short distance. With the wire held in place the needle is removed so as to avoid any damage to the wire during manipulation. The electrocardiographic leads are attached to the four extremities of the patient in the usual manner. The importance of properly grounding the recorder has been reported.[9,10] The bare tip of the wire is then connected to the V lead of the recorder by means of the alligator clips.

With electrocardiographic monitoring the wire is advanced and usually proceeds to the right atrium without difficulty. If the wire blocks in the region of the shoulder passage may be facilitated by withdrawing it a short distance and then readvancing. When a median arm vein is used there is rarely any difficulty in advancing the wire into the heart. The appearance of prominent P wave activity signifies that the electrode has entered the right atrium (Fig. 1). When the right atrium has been entered further advancement of the electrode 2 or 3 inches will usually allow the flow of blood to carry it into the right ventricle. If the P waves and QRS complexes decrease in amplitude after the electrode has been advanced this short distance it has either passed into the inferior vena cava or coiled back into the superior vena cava. P wave configuration may indicate which. When this happens the electrode should be withdrawn slightly so that it may re-enter the right atrium. When the electrode is moved back and forth over this short distance it will usually enter the right ventricle, where the P waves become very small and the QRS complex is greatly increased in amplitude (Fig. 1 *B*). When the right ventricle has been entered advancing the electrode an additional 1 or 2 inches will frequently allow the natural flow of blood to carry the platinum tip into the pulmonary artery. When this occurs the QRS complexes become small and the P waves remain small but may change their polarity (Fig. 1 *C*). The P waves may resemble those recorded in the right atrium if the electrode is passed out the pulmonary artery behind the right atrium. It should be emphasized that if the electrode does not enter the pulmonary artery after one has advanced it this short distance it is coiling and should not be advanced further but withdrawn slightly. Depending upon the location of the shunt in question the electrode is advanced to the desired position. If it is not possible to advance the electrode as desired fluoroscopy using an image intensifier may be helpful.

The hydrogen curves can be obtained with any standard electrocardiographic recorder. In this study both a Sanborn Visocardiette and an Electronics for Medicine recorder (using an AC amplifier) were used.

A small anesthetist's bag attached to a large three way valve and face mask is used for administering the hydrogen. The mask is held over the face with the patient breathing room air. By turning the valve one can deliver a single breath of hydrogen to the patient.

Fig. 1. Intracardiac electrocardiogram with platinum electrode wire. (Normal heart. L. H. 14, W.M. #452530.)

*The wires are available in lengths of [illegible] and 60 inches. The wires used in this study were kindly supplied by Davis and Geck Division of American Cyanamid Company, Danbury, Conn. (Product No. 12569-60).

The time of administration of hydrogen may be indicated by using the marker button on the electrocardiographic recorder Hydrogen curves may be repeated as many times as desired at intervals of 1 or 2 minutes If there is an early appearance of hydrogen in the pulmonary artery other curves may be obtained in more proximal chambers as well as the superior vena cava in order to localize the level of the shunt In the absence of any early appearance of hydrogen it is important that a recirculation curve be observed in order to confirm the sensitivity of the electrode If the appearance time is questionably early curves from more proximal chambers and the superior vena cava should be performed

When hydrogen is used the same precautions should be observed as with any flammable gas Because of its low density hydrogen tends to rise away from the operative field and is thus readily eliminated However all electrical equipment should be properly grounded In addition the anesthetist s bag and mask should be of conductive rubber and to insure that a static charge is not created on the bag or mask a ground wire is connected to the bag prior to filling it with hydrogen

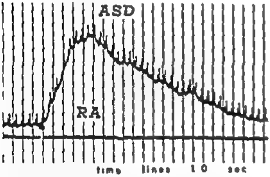

Fig 2A Positive hydrogen curve with platinum electrode wire recorded from the right atrium (RA) with the ECG channel in an Electronics for Medicine recorder ASD Atrial septal defect (M F 32F #187293)

Results

The following cases are presented to illustrate the simplicity and usefulness of this technique as an outpatient procedure as well as the excellent quality of records that may be obtained

Case 1 This 32 year old asymptomatic woman underwent evaluation for a heart murmur noted 1 year previously On physical examination there was a shock of the first heart sound with a slight thrust in the area of the third left intercostal space Auscultation revealed that the second heart sound in the pulmonary area was split and did not close with full expiration The pulmonary component was slightly increased Noted in this area was a short systolic ejection murmur which was somewhat louder at the lower left sternal border The electrocardiogram revealed right axis deviation with rsR pattern of mild right ventricular enlargement Chest films revealed a minimally enlarged heart with a slightly prominent main pulmonary artery and questionably increased vascular markings The right atrium was clearly enlarged The clinical impression was an atrial septal defect with mild pulmonary hypertension

The platinum tipped Teflon insulated wire was readily passed into the right atrium and a positive hydrogen curve confirmed the presence of a left to right shunt (Figs 2A and 2B) Subsequent curves from the superior vena cava were negative The patient subsequently underwent catheterization of the right side of the heart at which time a positive hydrogen curve was recorded in the right atrium with negative curves recorded from both cavae Of interest is the fact that the routine oxygen saturations were equivocal with but a 1 volume per cent difference between the cavae and the pulmonary artery This was reflected by a normal pulmonary arterial saturation of 68 per cent in association with a 67 per cent saturation in the inferior vena cava and a 58 per cent saturation in the superior vena cava Thus the sensitive hydrogen technique both localized the level and established

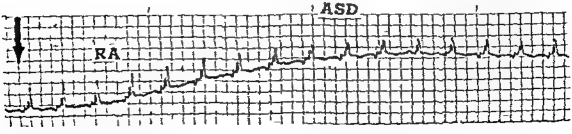

Fig 2B Positive hydrogen curve with platinum electrode wire recorded with a standard electrocardiographic recorder Sanborn Viso-Cardiette at a paper speed of 25 mm /sec (M F 32F #187293)

the presence of a shunt which by oxygen data was equivocal

The patient was subsequently operated upon using hypothermia and a secundum type of atrial septal defect which measured 2 cm in diameter was closed

Case 2 This asymptomatic 20 year-old man was first noted to have a murmur at 4 months of age Clinical evaluation when he was 14 years old suggested a large ventricular septal defect with mild pulmonary hypertension Catheterization revealed a pulmonary arterial pressure of 33/20 mm Hg and a large left to-right shunt at the ventricular level with a pulmonary arteriovenous oxygen difference of 1 59 volumes per cent When he was age 16 a 2 5-cm defect was closed with mattress sutures via the right atrium using cardiopulmonary bypass Three days after operation a loud systolic murmur reappeared and it was apparent that his defect was open This was confirmed by cardiac catheterization which revealed a pulmonary arterial pressure of 34/10 mm Hg with an infundibular chamber (not present at the first study) and a pressure in the body of the right ventricle of 70/0-6 mm Hg A left to-right shunt was demonstrated at the ventricular level with a pulmonary arteriovenous oxygen difference of 2 8 volumes per cent

At age 20 his only symptom being mild exertional dyspnea a second operation was performed The septum was visualized via a right ventriculotomy and the defect was noted to be widely open It was closed with a knitted Dacron patch After operation his systolic murmur was considerably less intense However follow up evaluation at 1 month revealed that the murmur had increased in intensity and at 2 months a systolic thrill was also noted Although it was possible that the murmur was secondary to the mild obstruction the fact that it had clearly increased in intensity suggested that the defect might have partially reopened Thus the electrode was passed into the right ventricular chamber where the positive hydrogen curves indicated that the defect was open (Fig 3)

Case 3 The 31 year-old asymptomatic man had had a diagnosis of infundibular–pulmonary stenosis which was confirmed by cardiac catheterization 8 years previously Blood gas studies suggested that there was no associated shunt On physical examination a systolic thrill was noted which was maximal in the third left intercostal space There was a slight right ventricular lift Auscultation revealed a systolic ejection murmur (Grade 4/6) which was maximal in the third left intercostal space and which was equally as loud in the second as in the fourth intercostal space The second heart sound in the pulmonary area was widely split but closed with full expiration No ejection click was heard and diastole was clear The electrocardiogram revealed right axis deviation with right ventricular enlargement A chest film revealed a prominent left pulmonary artery with normal appearing pulmonary vascularity

Because of the rarity of isolated infundibular–pulmonary stenosis and the inadequacy of routine oxygen data in ruling out a small cardiac shunt in such lesions[7] hydrogen curves were recorded in order to clearly establish the presence or absence of a small shunt The platinum tipped Teflon insulated wire was readily advanced into the pulmonary artery using the percutaneous approach As may be noted in Fig 4 the hydrogen curve from the pulmonary artery was negative showing only systemic recirculation thus establishing the diagnosis of isolated infundibular–pulmonary stenosis The patient subsequently underwent routine catheterization of the right side of the heart at which time similar hydrogen curves were recorded Right heart pressures again revealed only mild obstruction

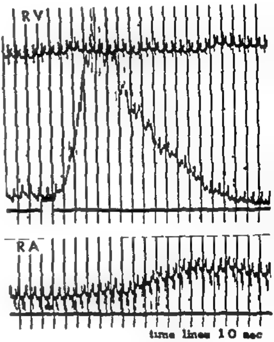

Fig 3 Hydrogen curves with intracardiac electrode wire recorded from the right ventricle (*RV*) and right atrium (*RA*) with an Electronics for Medicine recorder (Postoperative ventricular septal defect *J C 20 W M #91420*)

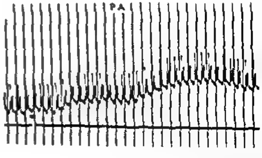

Fig 4 Negative hydrogen curve recorded from the *pulmonary* artery (*PA*) with an Electronics for Medicine recorder Time lines 1 0 second (Isolated infundibular–pulmonary stenosis F M 31 M #69887)

Case 4. This 8-year-old girl with a diagnosis of a small ventricular septal defect had been followed for 6 years. Cardiac catheterization when she was 4 years old had revealed equivocal oxygen saturations throughout the right heart. Auscultation revealed a high-pitched systolic murmur along the left sternal border, which was not particularly rasping. This murmur was Grade 3 (on a basis of 6) and maximum in the fourth left intercostal space. The murmur decreased on inspiration. The electrocardiogram and chest film were normal.

Because the oxygen saturation data had been equivocal during the previous catheterization, the sensitive technique of hydrogen was employed. With electrocardiographic monitoring the electrode was readily passed into the right ventricle and subsequently into the pulmonary artery. Figs. 5A and 5B show negative hydrogen curves which reveal only recirculation, thus establishing the presence *of a normal heart without any intracardiac shunts.* Subsequently, similar curves were obtained during routine right heart catheterization.

Discussion

The cases that have been presented illustrate the ease with which this technique may be used as an outpatient procedure to detect left-to-right intracardiac shunts. However, we are not advocating *that this technique be used by everyone* but only by those physicians who are cardiologists and specifically well versed in the clinical diagnosis of congenital heart disease. In the first, third, and fourth cases the oxygen data had been inadequate for establishing the presence or absence of small left-to-right shunts. However, hydrogen readily established the presence of an atrial septal defect in the first case and ruled out the presence of any left-to-right shunt in Cases 3 and 4.

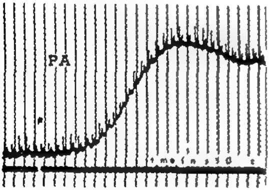

Fig. 5A. Negative hydrogen curve with platinum electrode wire recorded in the pulmonary artery (*PA*) with an Electronics for Medicine recorder. Systemic recirculation begins 5 seconds after inhalation of hydrogen. A curve from the superior vena cava had a similar appearance time. (Normal heart, V. T., SWF, #65187.)

Quantitation is not possible with the use of this electrical circuit, since the AC amplifier does not give a true curve. This is because the AC amplifier is constantly decaying base line shifts back to control levels. An advantage of this, however, is that the signal is returned to the base line rapidly and curves may thus be repeated with little delay. Also, in the AC amplifier with a high impedance (10 megohms in Electronics for Medicine ECG-EEG/phono channel and 5 megohms in the Sanborn ECG recorder) one has a very sensitive system for the detection of a *change* in potential at the electrode (appearance of hydrogen). *The AC amplifier of the Elec*tronics for Medicine Company is considerably more sensitive in the detection of a change in potential than their high-impedance (12 megohms) DC amplifier currently available for recording hydrogen curves. However, the DC amplifier does produce a signal which is representative of the changing potential at the electrode since it does not decay the signal as does the AC amplifier. Thus the DC system is necessary if any attempt at quantitation is desired. Hyman and associates[4] have suggested the use of a cathode follower with a 22 megohm impedance in conjunc-
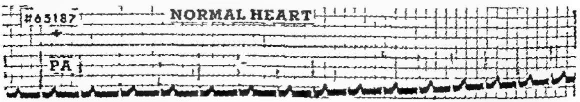
Fig. 5B. Negative hydrogen curve with platinum electrode wire recorded in the pulmonary artery (*PA*) with a standard electrocardiographic recorder (Sanborn Viso-Cardiette) at a paper speed of 25 mm./sec. Systemic recirculation is apparent after 8 heartbeats. (V. T., SWF.)

tion with a DC amplifier for recording hydrogen curves Whether their system is as sensitive as the high impedance AC circuit for detection of the appearance time of hydrogen at the electrode remains to be shown

Whenever clinical evaluation indicates the presence of a shunt routine cardiac catheterization is the procedure of choice if catheterization studies are desired However in the patient with borderline findings most likely normal but with a small shunt a possibility this technique has been most useful Also in the postoperative patient in whom murmurs may be difficult to interpret and in whom it is necessary to know whether the shunt is closed for proper care of the patient this technique has proved to be helpful This is particularly so when one does not desire to submit the patient to a full catheterization procedure in the immediate postoperative period

The recirculation time may be rapid especially in children In normal subjects aged 13 to 17 years we have observed an average value of 7 5 seconds for the main recirculation curve or after 6 to 10 heart beats[11] *In the presence of a small left to right shunt with normal pre sures the appearance time is usually within 1 to 2* seconds or after 1 to 3 heartbeats Also in the patient with a shunt the inflection of the hydrogen curve is brisk (see Figs 2*B* and 3) as compared to the recirculation curve which is slower rising (see Figs 4 and 5*A*) Occasionally a slight deviation of the base line may be noted (see Fig 4) prior to the main recirculation curve Whether this represents coronary flow or possibly early streaming via the kidneys is not clear However in the presence of shunts the initial deflection has always been of greater magnitude than the recirculation curve on the basis of our experience with over 1 500 curves in 300 patients during standard right heart catheterization

If there is any question about the significance of a deflection additional curves should be performed in the realization that movement of the patient may produce false deflections However through use of a 3 way valve with the bag only partially filled hydrogen may be administered without startling the patient which facilitates maintenance of a stable base line The hydrogen curves recorded with the Sanborn instrument are not so sharp as those recorded with the Electronics for Medicine apparatus This is because of the faster paper speed of the Sanborn instrument which slurs the upstroke of the curve

Just how small a shunt this technique will detect as we have used it is not clear Pathologic material is scarce since patients with very small shunts seldom come to operation at the present time However we have had the opportunity of examining the heart of an infant with evidence of a left to right shunt at the ventricular level by hydrogen only associated with a preductal coarctation of the aorta The patient died during operation and postmortem examination revealed a ventricular septal defect behind the septal leaflet of the tricuspid valve which would just admit the tip of a 1 mm probe Clearly the technique permits identification of small left to right shunts which has proved useful on many occasions[7]

The usefulness of this wire in evaluating complex arrhythmias has also been demonstrated on a number of occasions and has been found to be considerably easier to employ than the conventional technique of esophageal leads[8] A stable base line is easily achieved there is no trauma to the patient except for the discomfort of a simple venipuncture and it has been possible to enter the right atrium in all patients in whom a median vein was used

No complications have occurred attendant upon the use of this wire for either shunt or electrocardiographic analysis However caution must be exercised when the right ventricle is entered in that if sufficient wire is passed into the right ventricle or if the wire is left in the ventricle for a prolonged period a knot might possibly form in the wire or about a papillary muscle and/or chordae tendineae

Summary

A simple procedure for the detection of left to right intracardiac shunts is described A modification of the sensitive hydrogen–platinum-electrode system was employed

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Chronic ectopic tachycardia in infancy and childhood

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The clinical features of paroxysmal supraventricular tachycardia in infants and children have been reported previously from this institution.[1] The purpose of the present communication is to describe the cases of 10 children who had chronic ectopic tachycardias which lasted from 4 months to more than 10 years with characteristic features that clearly distinguished them from the usual textbook description of paroxysmal tachycardia. A comparison will be made between our patients and those reported on in the literature under such diverse titles as "ectopic auricular tachycardia,"[3] "auricular paroxysmal tachycardia with variable auriculoventricular conduction,"[4] "chronic auricular tachycardia,"[5] "persistent supraventricular tachycardia,"[6] and "repetitive paroxysmal tachycardia."[7] A simple classification is offered, and certain comments on the prognosis and therapy are made. It is hoped that such a report will focus attention upon this group of patients and thus lead the clinician to a more accurate appraisal of the prognosis as well as therapy.

Material and methods

Electrocardiograms of all patients discharged from Children's Hospital Medical Center between 1943 and 1960 with the clinical diagnosis of "atrial paroxysmal tachycardia due to unknown cause" were reviewed. Of 53 patients, 10 were found to have atypical electrocardiograms with persistence of the arrhythmia despite therapy from months to years. The clinical charts of these patients were reviewed, and an effort was made to trace those lost to follow-up. Appropriate electrocardiograms, x-ray films, and tests of thyroid function were obtained.

Case reports

The following cases illustrate many of the characteristic electrocardiographic and clinical features found in the spectrum of chronic ectopic tachycardia.

Case 1. D. W., a 14½-year-old boy with a chronic sustained atrial tachycardia, has been followed in our clinic for 9 years. He was first admitted to our hospital in 1953 with a 2 month history of fever, vomiting, and a cardiac rate unresponsive to digitalis or phenobarbital. Aside from a rapid rate which varied spontaneously in diurnal fashion, his physical examination as well as his chest x-ray and laboratory data were within normal limits. His electrocardiogram (Fig. 1) showed an ectopic atrial focus with a ventricular rate of 200 per minute. Despite a rapid ventricular rate with a 1:1 A-V response, P waves were visible in the limb lead and Lead V... During his first and several subse-

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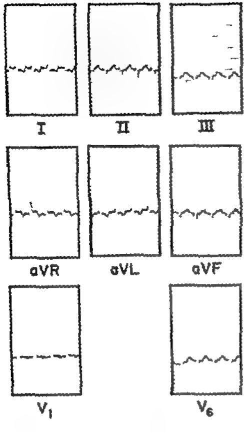

Fig. 1. Electrocardiogram of patient with sustained chronic supraventricular tachycardia. Atrial tachycardia of 200 per minute. ÂQRS = +60. ÂT = +60.

At hospital admission it was noted that his pulse rate showed marked variation depending upon the time of day and his state of consciousness. The electrocardiographic mechanism behind this was both a spontaneous slowing in the rate of the ectopic atrial focus and an increase in the degree of A-V block (Fig. 2). After being given an unsuccessful trial of digitalis, quinidine, and Prostigmine in conventional doses, he was discharged home on no drug therapy. For the next 15 months he remained in good health although his parents noted that his cardiac rate varied between 80 to 180 per minute. In 1955 he was readmitted to our hospital with clinical and radiologic signs of congestive heart failure (Fig. 3) associated with a sustained ventricular rate of 180 to 200 per minute. Digitalization slowed but did not abolish the ectopic focus. An additional complication was the occurrence of a complete hemiplegia of the left side on the fifth hospital day at a time when in spite of digitalis he still was having marked variation in his cardiac rate from hour to hour. In June 1956 after a prolonged period on digoxin and reserpine all medication was again discontinued whereupon a normal sinus rhythm returned. Thirteen months later when he made a routine outpatient visit the ectopic tachycardia was once again found to be present. He was hospitalized another time and finally discharged home on digoxin and reserpine which seemed to produce a steady rate with a persistent 2:1 A-V response albeit with the ectopic atrial focus unchanged. In February 1958 while he was on digoxin and reserpine normal sinus rhythm returned and was still present on his last checkup in March 1962. On digoxin he is in good health although signs of a residual hemiplegia remain.

We consider this patient to be representative of the group of patients who have sustained chronic supraventricular tachycardia with significant complications (cerebrovascular accident, congestive failure).

Case 2. F. L. is a 9 3/12 year old boy with no cardiovascular symptoms but with a chronic repetitive tachycardia who has been followed by us for 3¾ years. His irregular cardiac action was first discovered in March 1958 when he developed a cold. Physical examination, laboratory data, and x-ray films including cardiac fluoroscopy throughout the period of observation have remained normal. The stereotyped pattern of this patient's arrhythmia is related to his respirations (Fig. 4). On inspiration with speeding up of the sinus node the increased sinoatrial impulses are interrupted by a premature abnormal QRS complex, either a ventricular premature beat or an ectopic atrial beat with aberrant intraventricular conduction. This is followed by a burst of supraventricular ectopic beats which gradually decrease in frequency from 155 to 135 per minute. This terminates abruptly after one to twenty impulses and is usually followed by a return to sinus arrhythmia. During his first and second hospitalizations for purposes of conversion he received quinidine which only temporarily was effective in suppressing his ectopic activity. In recent months he has been on a program of digoxin and reserpine which in combination have kept him for the most part in normal sinus rhythm.

This patient is presented as a typical example of the repetitive form of chronic supraventricular tachycardia.

Case 3. G. M. is a 17½ year old girl was the subject of a separate report.[21] In 1950 at the age of 5 years she was first admitted to our hospital with a basilar skull fracture from which she recovered with no neurologic sequelae. Her physical examination, laboratory data, and chest film were normal. There was no past history of rheumatic fever, tachycardia, or cardiac disease. Her electrocardiogram (Fig. 5) showed bursts of ectopic beats with wide bizarre QRS complexes alternating with normally conducted impulses from the sinoatrial node, interpreted in the first report as a ventricular tachycardia.[21] Subsequently, because of the response to digitalis and vagal stimulation, an A-V nodal focus with atrioventricular dissociation and aberrant intraventricular conduction had been postulated. From 1949 to 1953 she was treated intermittently with quinidine sulfate. Blood levels in the range of 6 mg. per liter seemed to depress the ectopic focus. In 1954 quinidine was discontinued because of gastrointestinal symptoms and she was started on digitalis which similarly depressed but did not completely abolish ectopic activity. Other therapeutic maneuvers includ-

Prostigmine, antihistamines, anticonvulsant drugs, several trials of procaine amide, and unilateral stellate ganglion block have been unsuccessful. She has remained in excellent health even when off all medications for long periods of time, albeit with increased activity of the ectopic focus. There have been no signs of congestive heart failure, and her cardiac silhouette on x-ray examination has remained normal.

The beneficial effect of digitalis, plus the discovery of a response to reflex vagal stimulation, makes us think now that this arrhythmia should be classified as a chronic repetitive supraventricular tachycardia with aberrant intraventricular conduction.

Clinical profile

There were 6 boys and 4 girls in our group. The age of onset of tachycardia ranged from 6 days to 12 years (Table I). Vomiting and malaise accompanied by fever and epigastric pain were the most common presenting symptoms. Laboratory data were unrevealing in establishing an etiological diagnosis. Sedimentation rates, throat cultures, electrolytes, and tests of thyroid function were normal. Normal values for the red blood cell uptake of I[131] found in the 9 patients tested are noteworthy in light of reported elevated values in some patients with paroxysmal tachycardia and otherwise normal thyroid function.[39]

A survey of the electrocardiograms of our patients and of those reported by others in the literature suggests a distinct cardiographic profile, which distinguishes them from the ECG of paroxysmal atrial tachycardia. Characteristic features are variation in the frequency of the ectopic focus, a slower rate than usually seen in paroxysmal tachycardia, ease with which P waves can be identified in the standard leads, spontaneous occurrence of atrioventricular block, and susceptibility to extracardiac physiologic variables. Two broad categories of "repetitive" and "sustained" tachycardia may be distinguished. The ectopic focus in repetitive tachycardia manifests itself in bursts interrupted by sinoatrial beats (Fig. 1). With sustained tachycardia, although the rate of the ectopic focus may vary, sinoatrial activity is not apparent for long periods of time (Fig. 6).

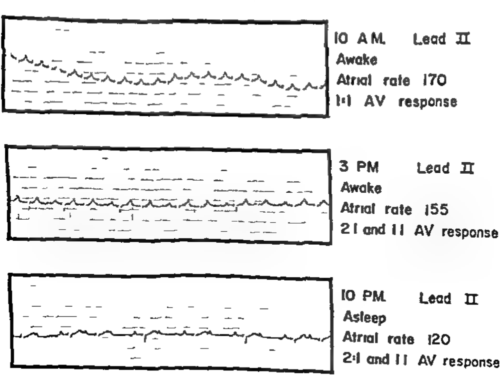

Fig. [illegible] Electrocardiogram of patient with sustained tachycardia demonstrating the mechanisms of changing ventricular rate.

Am Heart J
May 1964

Table I. Clinical profile of chronic ectopic tachycardia. Physical findings

Name	Sex	Age at onset	Presenting symptoms	Heart murmur	Cardiac enlargement	Duration of follow-up	Complications
			Repetitive				
G M	F	5 yr	Head injury	None	0	11[illegible] yr	None
R L	M	5 10/12 yr	Repeated U R I s	Grade I LLSB	0	3 4/12 yr	None
D M	M	6 days	Tachycardia found on routine E	None	0	3 9/12 yr	None
J M	F	[illegible] 7/12 yr	Vomiting, epigastric pain	None	0	1 9/12 yr	None
			Sustained				
S I	F	1 5/12 yr	Repeated U R I s edema	None	+2	4 4/12 yr	CHF
D W	M	5 11/12 yr	Vomiting, fever	None	+2	8 11/12 yr	CVS CHF
T P	M	[illegible] 10/12 yr	Vomiting	None	0	10/12 yr	None
R J	M	12 yr	Vomiting	Grade I LLSB	+1	1 3/12 yr	CHF
D Z		9 [illegible]/12 yr	Vomiting	None	0	4/12 yr	None
K B	F	[illegible]/12 yr	Tachycardia found on routine E	None	0	5 10/12 yr	None

Table II

Repetitive tachycardia

Name	Site of ectopic focus	Duration (number of ectopic beats/bursts)		Rate of ectopic focus		Diurnal change	Respiration	Crying
		B Rx	pRx	Range	Mode			
G M	V or N nodal	12 50	1-4	100-180	14[illegible]	0	[illegible]	–
D M	SV	Continuous	1 18	155 260	160	+	[illegible]	–
R L	SV	Continuous	2 5	130-175	155	0	+	–
J M	SV	Continuous	1 30	140 225	140	+	0	+

Sustained tachycardia

Name	Rate of ectopic focus		P waves visible	Diurnal change	Variation in rate with			
	Range	Mode			Respiration	Posture	Crying	Exercise
S I	1[illegible]0-20[illegible]	1[illegible]	+	[illegible]	0	+	+	+
D W	130-[illegible]	180	+	+	0	0	0	0
T P	100-1[illegible]0	1[illegible]0	+	[illegible]	0	–	0	–
R J	115 [illegible]	1[illegible]0	+	+	[illegible]	–	+	–
D Z	1[illegible]0-[illegible]15	1[illegible]	+	+	–	–	0	–
K B	100 [illegible]	150	+	+	0	–	–	+

[illegible] nodal. 0, No effect; +, Effect noted; –, [illegible]

In distinct contrast to patients with paroxysmal atrial tachycardia,[9] every one of our patients showed wide swings in the rate of their supraventricular focus from hour to hour, often in diurnal fashion (Fig. 2). The median increment of change in rate per 24 hours for our group was 80 per minute, with a range of 45 to 105 (Table II). The nodal rate was almost always slower than classic paroxysmal atrial tachycardia, with a median value of 155 per minute. In 6 of the 10 subjects this wide range in apical rate occurred in a definite day and night sequence (Fig. 2). The electrocardiographic mechanism behind this was threefold: (1) a slowing of the rate of the ectopic focus (all cases), (2) a decrease in or total absence of the number of ectopic beats during sleep (4 cases), (3) a spontaneous increase in the degree of atrioventricular block at night (1 case).

P waves in the electrocardiograms could be identified even at very rapid rates. The vector of the mean electrical P axis was usually but not always abnormal, ranging in all cases but 2 between +110 and −90 degrees. P-R intervals were greater than 0.12 second in 7 patients, fulfilling the usual criteria for an ectopic atrial focus.[5] In 2 cases a P-R interval of less than 0.12 second places them in the category of an atrioventricular nodal focus. In no instances could the atrial activity be defined as atrial flutter or fibrillation.

Equally striking was their responsiveness to physiologic hemodynamic changes (Table II). Patient S.L.'s ectopic focus was accelerated by exercise or emotion and slowed after rest in the supine position (Figs. 7 and 8). Atropine raised the rate of her ectopic focus from 160 to 196 per minute. Elevation of her blood pressure from 100/70 to 145/110 mm. Hg depressed it from 155 to 145. Pentolinium produced mild hypotension and a slight increase in the heart rate. After she was digitalized her ectopic focus showed a sustained pattern when she was standing but seemed to be partially suppressed when she was supine (Fig. 7).

Because of the spontaneous variation in the rate of the ectopic focus in chronic tachycardia, evaluation of the efficacy of drugs is particularly difficult (Table III). Cardiac glycosides tried at different times in all of our patients were thought to have some beneficial effect in every case either in slowing the rate of the ectopic focus (Figs. 4 and 5) or in increasing the degree of atrioventricular block. The use of quinidine in 7 patients temporarily abolished the ectopic focus in only 3. Reserpine in 3 of 5 patients was thought to have a beneficial effect. In 3 patients (S.I., C.M., R.L.) a variety of cardiotonic agents

Fig. 3. Serial x-ray films of patient with sustained tachycardia. Note the increase in heart size at the time of congestive failure (CHF). *Top*, Dec. 4, 1953, age 5 yr. and 11 mo.; heart rate 130-200. *Center*, March 31, 1955, age 6 yr. and 3 mo.; heart rate 200; CHF by physical examination. *Bottom*, Jan. 6, 195[illegible], age 10 yr.; heart rate 0-80; normal physical examination.

seemed to suppress ectopic activity, whereas in 2 others (T.P., J.M.) none of these drugs were definite benefit.

Fig. 9 represents in graphic form the clinical course of 6 of the 10 patients followed for more than 2 years. Of the 10 patients in our series only 3 in 1962 (Table III) had electrocardiograms which showed a normal sinus rhythm, and they were still on cardiac medication. Three of the 5 with sustained tachycardia developed cardiomegaly and congestive heart failure. It is of interest that congestive failure occurred in the context of sustained tachycardia in these 3 patients only during periods of time when there was loss of the diurnal variation in rate, and when the frequency of ventricular contractions was persistently greater than 180 per minute. In contrast, none of the 4 patients with repetitive tachycardia has shown signs of failure despite persistence of the arrhythmia for as long as 11½ years in one. That congestive heart failure need not imply a poor prognosis can be seen in that the 3 who were in failure were in good health in 1962, except for their ectopic focus, with follow-up periods varying from 4 months to 8 years. The occurrence of a cerebrovascular accident, probably secondary to a cerebral embolus associated with a rapid diurnal variation in rate in Patient D.W., represents the second case of this complication reported.[6] Despite the fact that 7 patients still have signs of ectopic activity, all have remained in good health with a normal cardiac size by physical and radiologic evaluation.

Discussion

The clinical picture of paroxysmal tachycardia was first described by Cotton[11]

Table III. Effect of drugs and present status

Name	Drugs					Present status	
	Digitalis	*Quinidine*	*Reserpine*	*Pronestyl*	*Prostigmine*	*Clinical*	*ECG*
				Repetitive tachycardia			
C. M.	+2	+3	—	0	0	Well on digitalis	Repetitive tachycardia still present
R. F.	+2	+3	+2	—	—	Well on digitalis and reserpine	Long runs of RT still present
D. M.	+2	—	—	—	—	Well on digitalis	RT still present
J. M.	+2	0	+1	—	—	Well on digitalis and reserpine	RT still present
				Sustained tachycardia			
S. L.	+1	+3	—	—	0	Well on digitalis and quinidine	Normal sinus rhythm
D. W.	+2	0	+1	—	0	Well but residual hemiplegia on digitalis	Normal sinus rhythm
T. P.	+1	[illegible]	—	—	—	Well on digitalis	Sustained tachycardia present
F. J.	+2	—	0	—	—	Well on digitalis	NSR. No sign of ectopic activity
D. Z.	+2	—	—	—	—	Well on digitalis	ST with 2:1 and 1:1 AV response
K. B.	+2	0	0	0	[illegible]	Well. No medication	ST appears on crying

Key to table: — = not tested; 0 = no effect; +1 = questionable benefit; +2 = benefit in slowing of ventricular rate; +3 = temporarily abolished ectopic focus; +4 = permanently abolished focus. NSR = Normal sinus rhythm; RT = Repetitive tachycardia; ST = Sustained tachycardia.

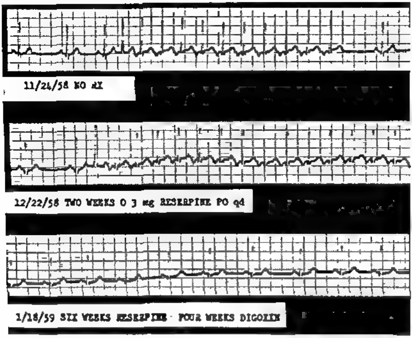

Fig 4 Electrocardiogram of patient with chronic repetitive tachycardia Note the appearance of burst in November and December of 1958 In January 1959 sinus rhythm prevailed

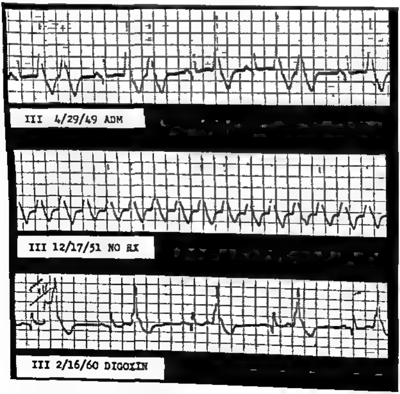

Fig 5 Electrocardiogram of patient with chronic repetitive tachycardia with intraventricular conduction disturbance Note the persistence of the ectopic focus through an 11 year period

seemed to suppress ectopic activity, whereas in 2 others (T.P., J.M.) none of these drugs were definite benefit.

Fig. 9 represents in graphic form the clinical course of 6 of the 10 patients followed for more than 2 years. Of the 10 patients in our series only 3 in 1962 (Table III) had electrocardiograms which showed a normal sinus rhythm, and they were still on cardiac medication. Three of the 5 with sustained tachycardia developed cardiomegaly and congestive heart failure. It is of interest that congestive failure occurred in the context of sustained tachycardia in these 3 patients only during periods of time when there was loss of the diurnal variation in rate and when the frequency of ventricular contractions was persistently greater than 180 per minute. In contrast, none of the 4 patients with repetitive tachycardia has shown signs of failure despite persistence of the arrhythmia for as long as 11½ years in one. That congestive heart failure need not imply a poor prognosis can be seen in that the 3 who were in failure were in good health in 1962 except for their ectopic focus, with follow-up periods varying from 4 months to 8 years. The occurrence of a cerebrovascular accident, probably secondary to a cerebral embolus associated with a rapid diurnal variation in rate in Patient D.W., represents the second case of this complication reported.[4] Despite the fact that 7 patients still have signs of ectopic activity, all have remained in good health with a normal cardiac size by physical and radiologic evaluation.

Discussion

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Table III. Effect of drugs and present status

Name	Drug					Present status	
	Digitalis	Quinidine	Reserpine[1]	Pronestyl	Prostigmine	Clinical	ECG
			Repetitive tachycardia				
G.M.	+2	+3	—	0	0	Well on digitalis	Repetitive tachycardia still present
I. I.	+2	+3	+2	—	—	Well on digitalis and reserpine	Long runs of RT still present
D.M.	+2	—	—	—	—	Well on digitalis	RT still present
J.M.	+2	0	+1	—	—	Well on digitalis and reserpine	RT still present
			Sustained tachycardia				
S.L.	+3	+3	—	—	0	Well on digitalis and quinidine	Normal sinus rhythm
D.W.	+2	0	+1	—	0	Well but residual hemiplegia, on digitalis	Normal sinus rhythm
T.P.	+1	0	—	—	—	Well on digitalis	Sustained tachycardia present
R.J.	+2	—	■	—	—	Well on digitalis	NSR. No sign of ectopic activity
D.Z.	+2	—	—	—	—	Well on digitalis	ST with 2:1 and 1:1 AV response
K.B.	+3	■	0	■	■	Well. No medication	ST appears on crying

Effect of drug: ■ = not tested; 0 = no effect; +1 = questionable benefit; +2 = beneficial slowing of ventricular rate; +3 = temporarily abolished ectopic focus; +4 = permanently abolished focus. NSR = Normal sinus rhythm; RT = Repetitive tachycardia; ST = Sustained tachycardia.

and Bristowe[29] at the end of the last century. Bouveret[31] can be credited with the introduction of the term "la tachycardie essentielle paroxystique" in 1889. Subsequently, the descriptions of Lewis, Hume, Campbell, and White clearly delimited the clinical, electrocardiographic, and prognostic features of this syndrome.[18, 31, 33] Pediatric aspects of paroxysmal tachycardia have been described by Hubbard, Nadas, and others.[1, 32, 33]

Although the majority of patients with paroxysmal tachycardia conform to the stereotype, many reports of atypical variants have appeared since the turn of the century.[4, 7, 11, 9, 10, 41] In 1947, Parkinson and Papp[7] reviewed the English and French literature and added 40 cases of their own of atypical paroxysmal tachycardia, 10 of which were in the pediatric age range. Their patients were described as having short paroxysms of atrial, nodal, or ventricular ectopic beats interrupted by normal sinus rhythm, continually present from months to years, a pattern which they termed "repetitive paroxysmal tachycardia." Despite its chronicity, they stressed the favorable prognosis; all of their patients remained in good health, with the longest follow-up being 18 years. Reports by Schachnow[4] and Hay[1] have stressed the distinction between the repetitive and sustained forms of chronic tachycardia, although Parkinson and Papp believed that at least in some a sustained tachycardia could be converted to a repetitive pattern with treatment (Fig. 6).[7]

If the 21 case reports of patients with chronic tachycardia who were less than 12 years of age are combined with the cases of our series, data are available on 31 patients, 18 patients with repetitive tachycardia and 13 with the sustained form. Of this total series, two thirds were males and one third females. All patients with sustained tachycardia had a supraventricular pattern, as did 16 of the 18 with the repetitive variant. In most cases

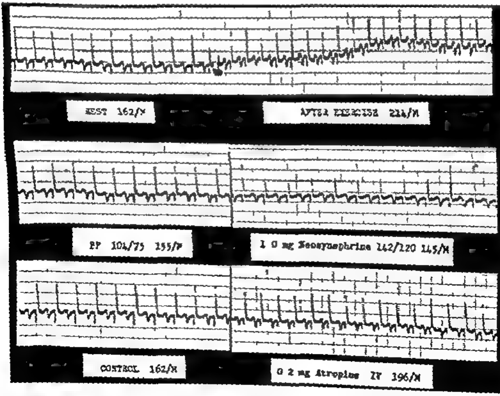

Fig. 5. Effects of exercise and drugs on sustained chronic supraventricular tachycardia. Note the increase in rate on effort and under the influence of atropine. Neo-synephrine caused slowing of the patient's heart rate.

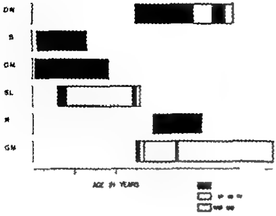

Fig. 9. Course of 6 patients with chronic supraventricular tachycardia who were followed for 5 years or more. Note that all of them still have some degree of tachycardia. CAT, Chronic atrial tachycardia; NSR, normal sinus rhythm.

at least part of the time relatively slow ectopic rates (less than 150 per minute) were recorded. A recurrent observation is their striking susceptibility to extracardiac influences, including position,[8,18] emotion,[40] carotid sinus stimulation,[3] time of day,[4] state of consciousness,[4] and even swallowing.[7] An analysis of the complications encountered in this combined series lends some justification to the separation of the repetitive and sustained forms. Whereas 7 of the 13 patients with sustained chronic tachycardia have shown signs of congestive heart failure, there has not been a single report of this complication in the group with repetitive tachycardia. Despite this, the long-term prognosis is not dissimilar. On the last evaluation all patients were in good health. In 10 of the 31 a normal sinus rhythm was found (4 sustained, 6 repetitive), although most were still on medication.

Despite the many case reports, few attempts have been made to consider the common characteristics of chronic ectopic tachycardia. Part of this hesitation has been a healthy reluctance to group these arrhythmias together, since cases do differ from one another with a greater range of variation than that of simple paroxysmal atrial tachycardia. The lack of a common etiological basis has also contributed to this heterogeneous viewpoint. Nevertheless, from a survey of those cases found in the literature, and from our experiences with the 10 patients herein reported on, we believe that a common clinical electrocardiographic profile emerges which justifies their inclusion under a single heading. Table IV, which lists the four theoretically possible combinations of site and pattern of arrhythmia, represents such a classification.

Table IV. Chronic ectopic tachycardia

A.	Chronic supraventricular tachycardia
	1. Sustained
	2. Repetitive
B.	Chronic ventricular tachycardia
	1. Sustained
	2. Repetitive

Summary

1. Ten patients with chronic ectopic arrhythmias have been reported on, some presenting with a sustained, others with a repetitive pattern.

2. The sustained and repetitive forms of chronic ectopic tachycardia should be grouped together, since transition from one to the other is relatively common.

3. Characteristic electrocardiographic features are variation in the rate of the ectopic focus, a relatively slow frequency in the range of 140 to 160 per minute, ease with which P waves can be identified in the standard leads, spontaneous occurrence of atrioventricular block, and susceptibility to extracardiac physiologic variables.

4. Characteristic clinical features are onset in childhood years, resistance to therapy, infrequent occurrence of congestive failure, cerebrovascular complications, and benign prognosis.

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Experimental and laboratory reports

Physical principles of artificial stimulation of the heart Stimulation of the canine heart in situ

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There are many methods of stimulation of the heart in case of cardiac arrest. To define our subject, we believe it is sufficient to mention the principal methods: (1) Stimulation of the heart by means of electrodes placed externally on the chest.[1] This method is very painful to the patient because of contraction of the skeletal muscles and irritation of the skin under the electrodes. (2) Direct stimulation of the heart by means of electrodes placed in or on the heart. In this case the electrodes can be connected with a stimulator placed externally or in the patient's abdominal wall. (3) Stimulation of the heart by means of an electrode mounted on the tip of a catheter that is placed in the right ventricle, with the other electrode in a thoracic subcutaneous position.[2] The stimulator is in an external position. This is the method used in our experiments. (4) Stimulation from a source that is located in an external position on the chest and connected inductively with an opposed coil which, with a rectifier, is sutured subcutaneously and connected by means of platinum wires to the myocardium.[3] The advantage of this method is that quantities such as frequency rate and current curve amplitude in milliamperes can be controlled and tested; this of course also applies to the first three methods mentioned.

The life of the batteries, infections, and mechanical defects still play a role of importance in these methods, so that further investigation and improvement are necessary. Artificial stimulation of the heart, however, has yielded methods entirely practicable from the point of view of physics.

Nevertheless, it must be borne in mind that a feature which is common to all these methods is their serious effect on the patient.

Some physical principles

A critical analysis of heart stimulation may be useful because there are indications of a degree of misapprehension in regard to the physical quantities involved in stimulation.

a. The passage of a current through the organism is associated with ion transport. Certain membranes in the body, when in the resting state, are passed more readily by K than by Na. At the passage of a current, a change in ion concentration can occur on one side of a membrane, and this may give rise to a physiologic action such as muscle contraction. It can be maintained in general that in the case of a direct current the physiologic influence is dependent on the local density of current, $\vec{J}$, which is defined as the charge passing per unit of time through a surface area

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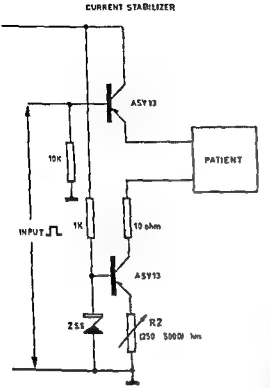

Fig. *1*. Current stabilization circuit with the patient in the circuit.

of 1 square centimeter perpendicular to the lines of flow and on the duration τ of the current passage.

Under a given intensity of current between the electrodes, even if its duration is unlimited, no reaction occurs (rheobase). Of course the intensity of current during the time should be reproducible and controllable, that is, it should not depend on various impedance variations in the tissue.

It is clear that for the purpose of heart stimulation a reproducible stabilized intensity of current between the electrodes should be applied during a time of the order of magnitude of a time characteristic of the heart, e.g., chronaxy. Rheobase and chronaxy of the myocardium will be discussed later. With a view to the spatial problems encountered in heart stimulation the density of intramyocardial current is the essential physical quantity (*not* as is often indicated in various publications and on instruments, the height of the pulse in volts). The latter may have dangerous consequences for the patient and must be rejected.

b. Obviously, stabilization of current is required in order to prevent distortion of the current curve in the tissue. Therefore the internal resistance of the pacemaker must be high relative to the patient's impedance and variations in impedance. The internal resistance of the pacemaker can be made high, say, by including in the patient's circuit a series resistance which is very high relative to the patient's variations in impedance. This, however, is an energy-consuming method.

A high effective dynamic R can be ensured by the transistor circuit shown in Fig. 1. As an example it can be stated that at a rectangular current pulse amplitude of 10 mA and with a patient's resistance varying from 100 Ω to 1 kΩ the R of this current amounts to 2×10 Ω. The amplitude can be regulated by means of potentiometer R. A current curve with an

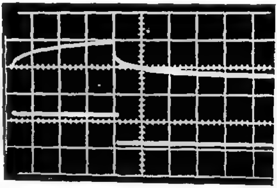

Fig. 2. *Upper curve:* Voltage with sensitivity 1 V/cm. *Lower curve:* Current with sensitivity 10 mA/cm. Time scale: 1 msec/cm. With current stabilization.

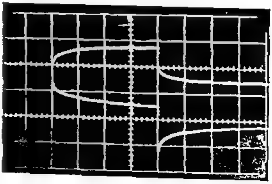

Fig. 3. *Upper curve:* Voltage with sensitivity 1 V/cm. *Lower curve:* Current with sensitivity 10 mA/cm. Time scale: 1 msec/cm. Without current stabilization.

amplitude of 20 mA is stabilized for 100 per cent at a load of 1 kΩ. This circuit therefore affords a high degree of stabilization to prevent distortion of current configuration. The direct voltage used to supply the transistors is 28 volts. Of course there are other arrangements to produce a high source impedance.

Fig. 2 shows a photographic record with the patient in the circuit with application of current stabilization. The current curve configuration is indeed rectangular.

Fig. 3 shows the distortion of the current curve with the patient in the circuit when no current stabilization is applied. Here the current pulse had become a sport of the processes in the tissues. There is no longer any question of a reproducible charge per rectangular pulse.

The intensity of current of every pacemaker can be studied as a function of load impedance.

Fig. 4 shows such a relation plotted for a commercial pacemaker with as parameter the intensity of current in milliamperes at 100 Ω. The stabilization of current is seen to be insufficient at greater load impedance.

As we pointed out, the method of Furman and Schwedel[8] was used in our experiments and applications. By electronic means the relation between current and voltage can be made visible on the screen of a cathode ray oscillograph while the patient is in the circuit. The quotient indicates the resistance (Ohm's law). When this method is used, the patient's resistance measured between the electrodes is

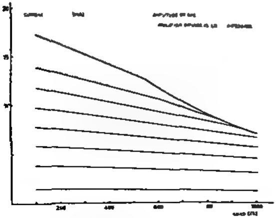

Fig. 4. Current intensity in milliamperes as a function of the load impedance.

Fig. 5. Electrodes *a* and *b* are suppliers of current. Electrodes *c* and *d* are voltage electrodes.

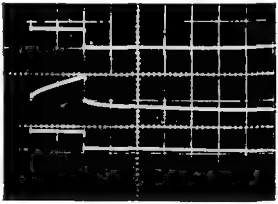

Fig. 6. *Upper curve*: Voltage measured between electrodes *c* and *d*. *Middle curve*: Voltage measured between electrodes *a* and *b*. *Lower curve*: Current measured between electrodes *a* and *b*. Sensitivity 0.2 V/cm. Time scale 1 msec./cm.

found to fluctuate between 100 and 200 Ω. With the implantable method of stimulation the initial resistance is 400 Ω and in some cases this increases within a few months to a few kΩs. This confirms the importance of stabilization of current.

It is clear that the initial resistance in the implantable method must exceed that in the Furman catheter method in view of the fact that the resistance of a spherical electrode placed in an electrolyte or in tissue is given by the equation

$$R = \frac{\rho}{4\pi r}$$

in which R = the resistance of a spherical

electrode placed in electrolyte or tissue, ρ = the specific resistance of electrolyte or tissue, and r = the radius of the electrode.

When an electrode is placed in electrolyte or tissue the resistance is determined chiefly by the radius r of the electrode. The maximum resistance is near the electrode and it is inversely proportional to the electrode radius; this explains the high initial resistance with the implantable method on the basis of the small r. Moreover, ρ tissue $\simeq$ 350 Ω cm $>$ ρ blood $\simeq$ 145 Ω cm.

d. It is worth while to note that a polarization effect on voltage occurs near the electrodes. To demonstrate this we used the so-called four electrode method in our experiments. As Fig. 5 indicates, four electrodes of V2A steel were inserted. Electrodes a and b are the suppliers of current, voltage is measured between electrodes c and d. The electrodes have a diameter of 1 mm. The voltage measured over c and d can be compared with the voltage measured between a and b. The experimental arrangement is shown in Fig. 5. The measurements were made on the right ventricle of the porcine heart postmortem.

The results of the measurements photographed from the oscillograph screen are shown in Fig. 6. The middle voltage curve was measured over a and b simultaneously with the lower (current) curve which has been stabilized. The voltage curve clearly demonstrates the influence of the polarization of the electrodes.

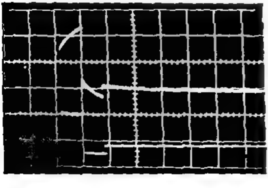

Fig. 7. Diphasic stabilized current curve. *Upper curve:* Voltage with sensitivity 0.2 V/cm. *Lower curve:* Current with sensitivity 5 mA/cm. Time scale 1 msec/cm.

e. When a direct current passes through an electrolyte substances are deposited on the electrodes. Faraday's law states that the quantity of substance deposited is exclusively dependent on the intensity of current, the time, and the nature of the substance. In artificial heart stimulation we are also dealing with electrolysis. To date little information is available in regard to the influence which electrolysis at the electrodes exerts on the tissue. Work on this subject has been done by Dittmar,[5] who studied the nature of the electrode

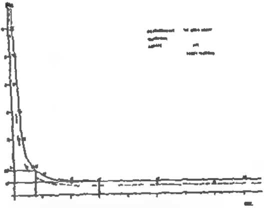

Fig. 8. Response of the canine heart with block to variations in curve duration and amplitude. Frequency rate 110 per minute. Position of electrodes: Inside right ventricular apex and subcutaneously in the thorax.

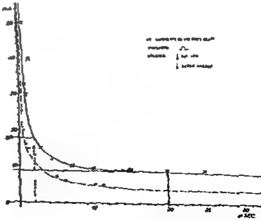

Fig. 9. Response of the canine heart with block upon variation of current curve duration and amplitude. Frequency rate 110 per minute. Position of electrodes: Outflow tract of right ventricle and subcutaneously in the thorax.

material in relation to its influence on adjacent tissue.

The question now arises whether the use of a diphasic current pulse would not be advisable. We did some experiments with the current curve shown in Fig. 7. The zero level of the curve is adjustable throughout the curve's amplitude. The diphasic current curve can be varied in duration, amplitude, and frequency rate, and of course has been stabilized. But a choice such as that shown in Fig. 7 virtually lacks compensation of polarization.

The experiments were carried out on canine and calf hearts in situ.

As a result of our observations, we can say that the heart in all cases showed a strong tendency to fibrillate; further investigation into the configuration of this curve is therefore desirable.

f. The hemodynamic consequences of stimulation open further avenues of investigation. The mode of contraction of the heart under the influence of a rectangular current pulse with adjustable duration and amplitude should be studied. The movements of the cardiac wall should be studied with the aid of electrokymograms. A study of the stroke volume of the heart could be made with the aid of an ultralow frequency ballistocardiograph or by the dye injection method.

Stimulation of the canine heart in situ with block

At this time, the question of why the heart contracts under the influence of a rectangular current pulse of given amplitude and duration cannot yet be answered. Experiments on the canine heart in situ with block, however, can teach us how contraction or noncontraction depends on current i and duration τ. For our experiments, A-V block was produced in a canine heart in the manner described by Meyler and associates.[6]

In our experiments we have attempted to answer the question whether it is possible to obtain a chronaxy-rheobase diagram of the heart. For this purpose an electronic unit was designed which is capable of supplying stabilized current pulses of rectangular configuration and adjustable amplitude, duration, and frequency rate.

The duration of the current pulse can be varied from 20 μsec to 1 second. Its amplitude can be varied from 20 μA to 100 mA. The frequency rate can be varied from 30 to 180 pulses per minute.

With a spherical electrode of V2A steel (ϕ 2 mm.) on the tip of a catheter in the apex of the right ventricle (− electrode) and another spherical electrode (ϕ 2 mm.) placed subcutaneously in the thorax, experiments with varying pulse duration and amplitude yielded the result recorded in Fig. 8.

The measuring points marked (x) indicate that the heart followed completely, whereas the measuring points marked ( ) indicate that the heart followed partly the imposed frequency rate.

With one electrode in the outflow tract of the right ventricle and the other implanted subcutaneously in the thorax, we obtained the result shown in Fig. 9.

The measurements warrant the following conclusions:

1. The values of chronaxy and rheobase are largely determined by the position of the electrode in the right ventricle. With the electrode in the outflow tract, the chronaxy was 2 msec. It was 0.8 msec. when the electrode was situated in the apex of the right ventricle. Fig. 8 shows that the rheobase was 0.5 mA with the electrode in the apex of the right ventricle; in the other location (Fig. 9), the rheobase

Fig. 10. Partial following of the imposed frequency rate in a canine heart with block in situ. Paper speed of 25 mm. per second. Lead V_6.

was 9 mA It is clear that the rheobase is a function of the electrode position The measurements were repeated in 3 different dogs with heart block and results were found to be reproducible with a 5 per cent variation

2 Changes in the position of the thoracic electrode within a radius of 15 cm proved to exert no influence on the results of measurement

3 Above and to the right of the drawn curve (Figs 8 and 9) the heart completely followed the imposed frequency rate The form of the drawn curve is

$$i = \frac{a}{t} + b$$

in which i is the intensity of current in milliamperes and t is the duration of the current curve in milliseconds while a and b are constants (This can be verified in the usual physical way by plotting $i \times t$ versus t)

4 Between the continuous and the interrupted curves the heart partly follows the imposed frequency rate In this respect the phase which the heart is in when the current pulse begins plays a role The heart is more sensitive to a stimulating impulse the longer ago was the previous spontaneous contraction This can be demonstrated by triggering on the QR flank of the QRS complex in a dog with a normal cardiac rhythm or with heart block and allowing a current pulse to arrive after an interval adjusted by electronic means Fig 10 illustrates this The peaks indicated by arrows represent the stimulating pulses

We also observed a pronounced difference in QRS duration between the provoked beats and the spontaneous beats The relation between chronaxy and rheobase on the one hand and phase on the other should be studied in more detail Important work in this respect has been done by Van Dam and associates[7]

Summary

1 In artificial heart stimulation the essential quantity is the density of current $\vec{J}$ in the intramyocardial wall Dosage of the pulse amplitude in volts can have serious consequences for the patient. Curve indications in volts on pacemakers and in publications and records must therefore be rejected

2 Hence the pacemaker should supply stabilized current pulses even while the load impedance is increasing

3 The distortion of the voltage curve at stabilized current is an electrode effect

4 Separate measurement and registration of the physical quantities involved in stimulation is advisable The values obtained in every individual patient warrant conclusions as to the method of choice It is recommended that one start with the Furman and Schwedel method i e with one electrode in the right ventricle and the other placed subcutaneously in the thorax (a noncritical location)

5 Measurements on the canine heart in situ with block carried out with currents pulses of rectangular configuration revealed that when the Furman method is used chronaxy and rheobase of the myocardium are dependent on the position of the electrodes

6 The phase which the heart is in when the current pulse is supplied is a factor of importance for the heart s following of the imposed frequency rate

I wish to thank Professor J Wieberdink M D and G T Meester M Sc for the surgical contribution to this study and Messrs H G Govaerts M J de Jager and W A van Beek for electronic and technical assistance

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The relationship of left atrial pressure and volume in patients with heart disease

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Left atrial pressure and left atrial volume both vary over a considerable range of magnitude in patients with heart disease.[1-4] Mitral valve disease and left ventricular failure are the most common conditions in which left atrial pressure and volume are increased. Soloff and co-workers[5] were unable to demonstrate a relationship between pulmonary capillary pressure and an index of left atrial volume in patients with mitral stenosis. The present study is concerned with the relationship of left atrial pressure and volume in patients with mitral stenosis, mitral insufficiency, aortic valve disease, or idiopathic cardiomyopathy.

Materials and methods

Thirty-nine patients were studied by left heart catheterization and angiocardiography. The clinical diagnoses of these patients are listed in Table I. Patients with combined mitral stenosis and insufficiency were classified as having mitral insufficiency if the regurgitant flow exceeded 35 ml. per beat. The degree of mitral insufficiency was defined by the difference between the left ventricular stroke volume as calculated from biplane angiocardiograms and forward stroke volume determined by the Fick or indicator dilution methods.[6]

All patients were studied in the fasting, resting, recumbent state. Left atrial pressures were recorded through catheters introduced into the left atrium by the transbronchial or transseptal methods.[7,8] Zero reference for pressure was taken at a point 10 cm. above the backs of the recumbent patients. Recordings of pressure were obtained during or shortly before angiocardiography, using strain gauge transducers and a direct-writing multichannel recorder. Mean left atrial pressure was obtained by electrical integration of the atrial pressure curve. Pulse pressure was taken as the difference between the highest and the lowest left atrial pressures within a cardiac cycle. The peak v wave pressure is used in this study to indicate the maximum level of atrial pressure above the zero reference at the peak of the v wave.

Left atrial volumes were calculated from biplane angiocardiograms taken at 4 to 6 pairs of films per second in the anteroposterior (a.p.) and left lateral projections

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Fig 1 Anteroposterior (*A*) and lateral (*B*) films of a postmortem heart with the left atrium distended with contrast material The dotted lines represent the longest measured diameters in the two projections On the anteroposterior film the line traces the margin of the atrium and is drawn across the base of the projection of the atrial appendage excluding the latter from the area to be measured

Schonander biplane film changer was used Contrast material (usually 75 per cent Hypaque*) was injected with a Gidlund power syringe into the left atrium in 14 patients and into the right side of the heart in 20 patients In 5 patients with mitral insufficiency left ventricular injection resulted in opacification of the left atrium The method used for calculating left atrial volume from biplane films is based on the assumption that the left atrium can be represented by an ellipsoid reference figure and is similar to a method previously described for determining left ventricular volume [9] Pairs of films were used which showed satisfactory opacification of the left atrial chamber in both the a p and left lateral projections The outline of the left atrium was traced on each film excluding the atrial appendage The area of the atrial image was determined by planimetry and the maximum distance across the traced atrial image or major axis was measured directly on each film The minor axis on each film was calculated from a transposition of the formula for the area of an ellipse

$$b = \frac{4A}{\pi a}$$

where b = minor axis A = area of left atrial image and a = major axis The axes thus obtained were corrected for distortion due to nonparallel x rays The correction factors used to correct for this distortion were derived from the known x ray tube to film distances and the distances of the estimated center of mass of the left atrium to the films as described previously [9]

The volume of the atrium was calculated by inserting the corrected axes from each pair of a p or lateral films into the formula for the volume of an ellipsoid

$$V = \frac{4}{3}\pi \quad \frac{a'}{2} \quad \frac{b}{2} \quad \frac{c'}{2}$$

where V = volume of ellipsoid a′ = longest corrected major axis whether on the a p or lateral film b = corrected minor axis of the a p film c = corrected minor axis on the lateral film

*Hypaque Winthrop Laboratories New York N Y

This method for quantifying left atrial volume and changes in volume has been tested in studies performed on 22 human postmortem hearts. The intact hearts were removed at autopsy and the pulmonary veins were sutured closed at the junction with the left atrium. A cannula for injecting contrast material was tied into one pulmonary vein. The left ventricle was incised to expose the ventricular aspect of the mitral valve and the leaflets of the mitral valve were clamped closed along the line of normal closure. The specimen was suspended on a Schonander biplane film changer so that both position and distances with respect to films and x ray tubes approximated those existing during angiocardiography in vivo when films are taken in the a p and left lateral projections. Known increments of barium sulfate paste were injected through the cannula into the left atrium and biplane films were taken at each volume. Successive 10 to 30 ml increments of barium sulfate were added until the preparation developed a leak. The margins of the left atrium on the a p and lateral films were traced excluding the atrial appendage as illustrated in Fig. 1. Measurements were corrected for distortion due to nonparallel x rays and volumes were calculated by the same methods described earlier. Calculated left atrial volumes were compared to known left atrial volumes as shown in Fig. 2 which

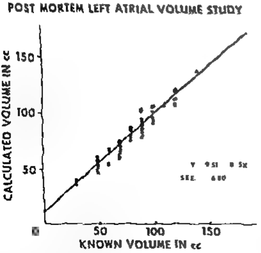

Fig. 2. Calculated left atrial volumes are related to known left atrial volumes.

illustrates 85 observations on the 22 postmortem hearts over a range of volumes of 30 to 160 ml. Known and calculated volumes were related by the following regression equation:

$y = .895x + 9.51$ (as shown in the figure) or known volume = 1.12 calculated volume − 10.6 ml.

The standard error of estimate was ± 6.8 ml. This regression equation was applied to correct the calculated atrial volumes in the studies of patients.

The results of the postmortem studies were also analyzed in terms of the accuracy of the method for determining changes in left atrial volume within the same heart. Known increments in volume were 10 to 30 ml between successive films. The following regression equation expresses the relationship between known and calculated volume changes:

Known volume = 1.29 calculated volume − 1.7 ml.

The standard error of estimate was 3.5 ml.

In studies of patients biplane films from 3 to 5 successive heart cycles usually demonstrated satisfactory left atrial opacification and permitted calculation of volume. During angiocardiography all films were timed with respect to the electrocardiogram.[4] The volume calculated from each pair of films was plotted according to the time of film exposure within the cardiac cycle. By a plotting of all atrial volumes for a given patient with respect to time from onset of QRS and as though all films had been taken within a single cardiac cycle a composite atrial volume curve was constructed. For each patient 7 to 28 (average 18) pairs of biplane x ray films demonstrated adequate opacification of the left atrium and were used for calculation of volume and construction of a composite volume curve. From the composite volume curve change in left atrial volume or stroke volume was calculated as the difference between maximum and minimum atrial volumes. Mean left atrial volume was derived from the volume curve by planimetric integration.

Ten patients had atrial fibrillation with mean ventricular rates varying from 70 to 100 per minute during angiocardiography and with R-R intervals which varied from beat to beat. In these patients atrial vol

Mean pressure and mean volume correlated significantly in the patients with aortic stenosis or with primary cardiomyopathy (i.e. patients without mitral valve disease). Peak v wave pressure and maximum volume correlated significantly in patients with mitral stenosis and again in patients with aortic stenosis or primary cardiomyopathy. Neither mean pressure-mean volume nor peak v wave pressure-maximum volume correlated significantly in patients with mitral insufficiency, bivalvular disease, or in all patients considered together. Pulse pressure showed no significant correlation with either maximum volume or stroke volume in any of the groups of patients.

Discussion

In this study no correlation was demonstrated between mean left atrial pressure and mean volume in patients with mitral valve disease. *This finding is similar to* that described earlier by Soloff and coworkers, who were unable to demonstrate a correlation in patients with mitral stenosis between pulmonary wedge pressures

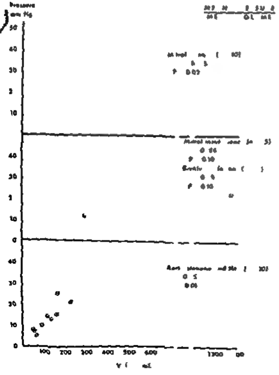

Fig. 3. Relationship between mean left atrial pressure and volume in three groups of patients.

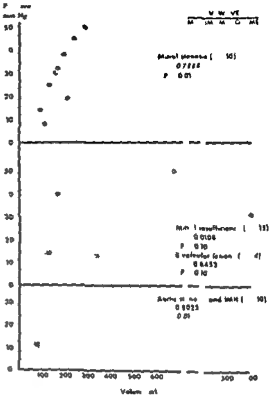

Fig. 4. Relationship between the peak v wave pressure and maximum left atrial volume.

and relative left atrial volume indices derived from biplane angiocardiograms. These authors concluded that factors other than pressure were responsible for the increase in atrial volume and speculated that changes in the elasticity of the left atrial wall, possibly from rheumatic fever, might be an important determinant of atrial enlargement.

The present study does not clarify the reasons for the lack of correlation between left atrial volume and mean pressure as observed in patients with mitral valve disease. However, in patients with mitral stenosis maximum left atrial volume and the pressure at the peak of the v wave were correlated, which suggests that this component of atrial pressure may be important in determining atrial volume in this group of patients. As illustrated in Tables I and II, the patients with mitral insufficiency had as a group larger left atrial volumes than those of the patients with mitral stenosis. This difference in volumes could not be related to the difference in pressures as recorded at the time of these studies

In patients with mitral insufficiency no correlation was found between left atrial volume and any of the left atrial pressure values investigated here mean pressure, pressure at the peak of the v wave, or left atrial pulse pressure. Therefore, factors other than the left atrial pressure values found at the time of these studies must have been important in determining the large left atrial volumes observed in this group of patients with mitral insufficiency. Such other factors might include the following: duration of disease, direct involvement of the atrial wall by disease with resulting atrial dilatation, or more marked elevation of atrial pressure at certain times during the course of the chronic heart disease, e.g., during physical activity. In regard to the possibility of factors other than pressure which may be relevant in determining left atrial volume, two of the patients, J.M. and L.M. (Table I), are of particular interest. Each of these patients had developed acute mitral insufficiency as a result of rupture of chordae tendineae approximately 3 months prior to study. Only modest left atrial enlargement was observed in these two patients in spite of

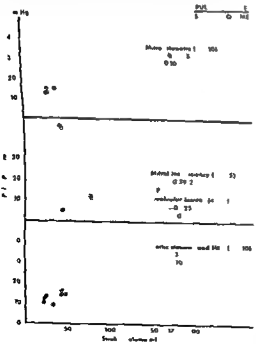

Fig. 5 Relationship between left atrial pulse pressure and stroke volume.

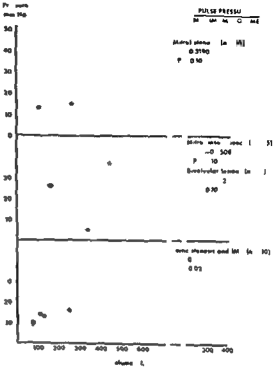

Fig. 6 Relationship between left atrial pulse pressure and maximum left atrial volume.

greatly elevated left atrial pressures. Thus an elevated left atrial pressure per se did not result in marked left atrial enlargement over a period of a few months.

In patients with aortic stenosis or primary cardiomyopathy who were grouped together on the basis of absence of mitral valve disease, left atrial pressure and volume were correlated. Here again only moderate left atrial enlargement was observed in patients with elevated left atrial pressure. Pronounced enlargement of the left atrium so common in the presence of mitral insufficiency was not seen in these patients even though some of them had pressures in the same range as those of patients with mitral valve disease. The elevated left atrial pressure found in these patients without mitral valve disease was a manifestation of left ventricular failure or altered left ventricular distensibility. Accordingly, the elevation of left atrial pressure was probably of relatively short duration compared to that observed in patients with chronic rheumatic heart disease with mitral insufficiency. Again it is of interest that the two patients with

tral valve insufficiency of recent onset had relationships between mean left atrial pressure and volume that were similar to those observed in the patients without mitral valve disease. In fact, in the two patients with acute mitral insufficiency and in these patients with left ventricular failure or altered ventricular distensibility and without mitral valve disease, it appears that one could make a reasonable estimation of mean left atrial pressure from knowledge of the mean left atrial volume.

Summary

The relationship between left atrial pressure and volume was studied in 39 patients with valvular heart disease or idiopathic cardiomyopathy. Left atrial pressure and left atrial volume were correlated in patients with aortic stenosis or with idiopathic cardiomyopathy. Patients with mitral stenosis showed a correlation between pressure at the peak of the v wave and maximum left atrial volume. No correlation between left atrial pressure and volume was found in patients with mitral insufficiency.

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Anaerobic metabolic responses to acute maximal exercise in male athletes

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Energy for muscular exercise is derived from both aerobic and anaerobic metabolic pathways. The magnitude of the former is represented by the oxygen intake, whereas that of the latter is manifested by the oxygen debt and accumulation of lactate.[1] Whenever circulatory transport of oxygen is either delayed or insufficient, intracellular oxidation-reduction systems shift toward the reduced state. This results in increased reduction of pyruvate to lactate, with the concomitant regeneration of DPN from DPNH. Huckabee[2] differentiated excess lactate from other mechanisms of lactate mobilization and used this excess lactate to derive a quantitative expression of the anaerobic metabolic rate in terms of an equivalent intake of oxygen. Summation of the observed intake of oxygen and the anaerobic rate provided an estimate of the total energy metabolism. At low levels of exercise of short duration, the proportional contribution of aerobic to total metabolic responses, or per cent response of intake of oxygen, as defined by Huckabee and Judson,[3] revealed distinct differences between normal subjects and patients in heart failure. Indeed, this disparity suggested a fundamental difference in mechanisms of energy supply between these two groups which, within the limits studied, was largely independent of the severity and duration of effort. An opportunity to test this hypothesis was provided in this laboratory by the studies of Cobb and Johnson,[4] who strenuously exercised sedentary and physically trained men by walking them at 3 miles per hour (mph) and 18 per cent grade. Mean oxygen intakes and cardiac outputs, corrected for body size, were identical for both groups. Yet the physically trained men continued exertion for over an hour without fatigue or significant accumulation of lactate, whereas the sedentary men became exhausted within half an hour and exhibited marked elevation of lactate in arterial blood. The 94 per cent response of oxygen intake in the trained men and 80 per cent response in the sedentary men were comparable to the values reported by Huckabee and Judson for normal subjects and patients in heart failure, respectively. These findings prompted further investigation to ascertain the per cent response of oxygen

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intake of athletes to maximal exertion and also the effects of submaximal work loads utilizing different types of exercise

Material

Physical characteristics of 3 groups of normal young men are shown in Table I Group I was subdivided into 10 former (recent) varsity athletes (IA) and 5 graduate students in physical education (IB) Groups II and III included both varsity athletes and normal men who participated in sports Four men in both Groups II and III were studied on separate occasions

Table I Physical characteristics of normal men

Group	*Physical conditioning*	*Age (yr)*	*Height (cm)**	*Weight (Kg)*
IA	Former varsity athletes	25 8(21 32)	182(178 188)	83 1(61 91)
IB	Active physical education majors	23 8(21 26)	1 5(175-183)	71 0(57 77)
II	Varsity track basketball football pentathlon and other sport athletes	22 6(18 31)	184(173 194)	78 4(63 92)
III	As above	21 5(19 24)	181(165-190)	79 9(65 93)

*Mean (Range)

Table II Responses to acute maximal exercise (after an initial submaximal exertion for 3 minutes) in Group I normal men

	Subgroup A (former athletes—10)	*Subgroup B (active normals—5)*
Heart rate	195(175 220)	198(193-212)
Oxygen intake (L /min)	3 85(2 74-4 0)	3 09(2 75-3 39)
Oxygen intake (ml /kg)	47 3(34 8 62 0)	44 5(38 8-48 7)
Oxygen pulse (ml /kg)	25(17- 31)	22(18 25)
Excess lactate (mM /L)	8 7(5 3 15 4)	7 9(4 2 9 7)
Anaerobic rate (L /min)	1 2(72 2 20)	96(56-1 44)
Anaerobic rate (ml /kg)	14 6(8 2 25 3)	12 1(8 8 17 6)
Oxygen pulse deficit (ml /kg)	− 07(05 12)	− 07(05 09)
Aerobic response (%)	76 5(63 0 88 3)	75 0(63 7-86 2)
Duration (minute)	5 1(4 1 6 2)	5 3(3 0-9 0)

Mean (Range)

Table III Responses to acute maximal exercise in normal men*

	Group II—10 subjects (running on treadmill)	*Group III—11 subjects (sitting on bicycle ergometer)*
Heart rate	188 ± 13	184 ± 16
Oxygen intake (L /min)	3 6 ± 7	3 4 ± 5
Oxygen intake (ml /kg)	48 ± 12	43 ± 8
Oxygen pulse (ml)	19 1 ± 4 2	18 9 ± 3 4
Excess lactate (mM /L)	10 7 ± 3 1	8 7 ± 2 2
Anaerobic rate (L /min)	−1 4 ± 0 6	− 9 ± 4
Anaerobic rate (ml /kg)	−18 ± 7	−11 ± 5
Oxygen pulse deficit (ml)	−7 1 ± 3 4	−4 7 ± 2 4
Oxygen pulse deficit (ml /kg)	− 10 ± 03	− 06 ± 03
Total metabolic rate (L /min)	5 0 ± 0 8	4 3 ± [illegible]
Aerobic response (%)	71 ± 11	78 ± 7
Anaerobic response (%)	28 ± 11	20 ± 7
Duration (minute)	2 6 ± 7	3 6 ± 1 4

*Immediately after consecutive work loads of increasing severity expressed mean ±standard deviations

Each was tested from 1 to 3 hours after a light meal; only 1 had participated in vigorous physical activity just prior to the testing.

Methods

Subjects in Group I walked on a treadmill at 5 mph and 18 per cent grade for 3 minutes prior to running at 6.5 mph and 25 per cent grade until exhausted. Group II subjects were studied while walking at 1.7 mph and 10 per cent grade, 3.4 mph and 14 per cent grade, and 5.0 mph and 18 per cent grade, each for 3 minutes prior to running at 6.0 mph and 22 per cent grade until exhausted. Each man stood at rest for 15 seconds between work loads while the speed and grade of the treadmill were changed and blood was sampled. Those in Group III pedaled a bicycle ergometer without interruption. The work load was increased every 5 minutes until exhaustion, starting at 150 kilogram-meters per minute (Kpm) and increasing as follows: 500, 1,000, 1,250, 1,500, and 1,750 Kpm. Maximum work load ranged from 1,000 to 1,750 Kpm in these men.

Heart rates were recorded from a precordial electrocardiogram. Oxygen intake was estimated from expired air collected with a low resistance face mask and valve system utilizing a 150 liter spirometer and a Beckman analyzer. Collections were made during the last 60 seconds of each submaximal exercise period* and for 30 seconds of maximal exertion *after* the subject signaled that he was exhausted but while exercise continued. Only a few were able to continue exertion for seconds after this sampling.

Samples of blood from subjects in Groups IA and IB were obtained with an indwelling needle in a forearm vein immediately after maximal exertion. (Since the oxygen saturation—Van Slyke and Neill—exceeded 98 per cent at this time, this source was markedly arterialized.) Samples from men in Groups II and III were obtained with a Cournand needle placed in the radial or brachial artery prior to exercise. Blood was withdrawn at rest and at the end of each period of exercise into heparinized syringes and immediately precipitated in ice-cold 10 per cent trichloroacetic acid. Concentrations of pyruvate and lactate were determined by standard methods.[5,6]

Excess lactate (XL) was derived according to Huckabee's method:

$$XL = \Delta L - \Delta P\,(L_o/P_o) \qquad (1)$$

and converted to anaerobic metabolic rate (AMR) or equivalent quantity of oxygen intake represented by the excess lactate as follows:

$$AMR = \frac{(\Delta XL)\ (\text{Body water})\ (11.2)}{\Delta t} \qquad (2)$$

where ΔL and ΔP represent the change in the concentrations of lactate and pyruvate in millimoles per liter of blood water* from rest to end of each exercise period and L_o/P_o represents the ratio of initial resting concentrations. Serial changes in excess lactate (ΔXL) represent the *sequential* change in calculated XL from one exercise period to the next which was conducted at a higher work load. Body water in these muscular nonedematous young men was assumed to be 60 per cent of the body weight, an arbitrary value between the averages reported by antipyrine and deuterium-oxide methods.[7] Total metabolism was derived from the sum of oxygen intake (STPD) and AMR (each corrected for body weight); per cent responses of AMR and $\dot{V}_{O_2}$ were related to this estimated total metabolic response.

Results

I. Acute maximal exercise (running 6.5 mph at 25 per cent grade). Heart rate and metabolic responses to acute maximal exercise in men in Group IA and IB are presented in Table II. The mean duration of maximal exercise was just over 5 minutes. Ventilation averaged 116 with a range of 81.0 to 136.2 L. per minute. Concentration of lactate averaged 102 mg. per cent, whereas excess lactate rose to an average of 8.7 and 7.9 mM per liter of blood water for the two subgroups.

The interrelations of mean heart rate, oxygen pulse, and apparent deficit in oxygen pulse are displayed in Fig. 1. Since

*In experiments on 10 other subjects, submaximal work loads were continued for an extra 3 minutes in order to permit repetition of measurements of intake of oxygen. Since there were no significant changes, a reasonable approximation of a steady state had been achieved.

*Water content of whole blood was assumed to be 0.8.

the metabolic need was in excess of circulatory capacity for oxygen transport, the aerobic contribution to total metabolism in these 2 subgroups averaged only 75 and 78 per cent, and it was less than 86 per cent in all instances.

2. *Work loads of increasing severity on a treadmill.* Mean heart rates and metabolic responses under these experimental conditions are presented in Table III and Fig. 2. Although the duration of maximal exertion was less than 3 minutes, it should be noted that this followed 9 minutes of submaximal exertion of progressively increasing stress. Mean heart rate increased from 90 at the lowest work load to 188 per minute with maximal exertion. Maximal ventilation and oxygen intake averaged 119 and 3.6 L. per minute, respectively. Concentrations of lactate and pyruvate at the onset of recovery were 104 ± 25 and 1.9 ± 0.3 mg. per cent; excess lactate averaged 10.7 ± 3.1 mM/L. The increase in excess lactate from the preceding submaximal exercise was equivalent to an anaerobic metabolic rate of 1.4 L. per minute. Accordingly, the per cent response of oxygen intake to total metabolic responses diminished progressively with each increment in work load to a final value of 71 per cent for maximal exertion.

3. *Work loads of increasing severity on a bicycle ergometer.* Since in these experiments the subjects were seated on a bicycle, only part of the weight of the body was supported by the legs. Average responses are shown in Fig. 3 and Table III. Although the total duration of exercise was longer, the maximal rate of oxygen intake of 3.5 L. per minute was nearly the same as observed with exercise on the treadmill. Mean heart rate increased from 97 at the lowest to 181 per minute at the highest work load. Ventilation, however, averaged only 83.1 L. per minute. Lactate and pyruvate reached 81.3 ± 18.8 and 1.12 ± .53 mg. per cent, respectively. Excess lactate averaged 8.7 ± 2.2 mM per liter, and the mean per cent response of oxygen intake was 80 per cent.

Four subjects were studied both on the bicycle ergometer and on the treadmill (and the findings are included in results for Groups II and III). Examination of

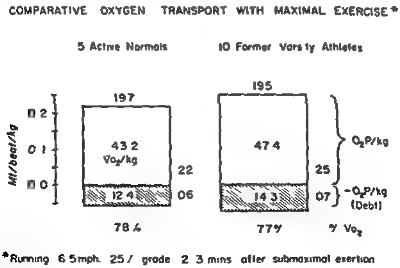

Fig. 1. Graphic display of average circulatory transport of oxygen during acute maximal exercise in 5 active normal men (physical education majors) and 10 former (recent) varsity athletes. Area of open rectangles represents oxygen intake expressed as ml./Kg. of body weight per minute; abscissa represents maximal heart rate, whereas ordinate represents maximal oxygen pulse per Kg. Shaded rectangle represents anaerobic metabolic rate (AMR) derived from measurements of excess lactate and apparent deficit in oxygen pulse in ml./Kg. derived by dividing the AMR by the heart rate. Note the relatively low value for per cent response of oxygen intake and the magnitude of the anaerobic response under these conditions. This maximal exertion lasted for 2 or 3 minutes.

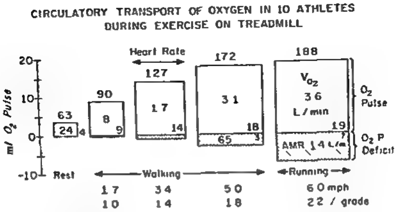

Fig 2 Serial changes in heart rate oxygen pulse and oxygen intake in L /minute for 10 physically active men during work loads of increasing severity on the treadmill Note the progressive rise in anaerobic metabolism with increasing exercise Only 15 seconds of rest was permitted between each 3 minute work load terminally the men ran for about 2 5 minutes until exhausted Values for oxygen intake and oxygen pulse (plotted in lower right hand corner of open rectangles) are expressed as L /minute and ml /heart beat respectively Similarly AMR and deficit in oxygen pulse represented as negative values are also expressed as L /minute and ml /heart beat respectively

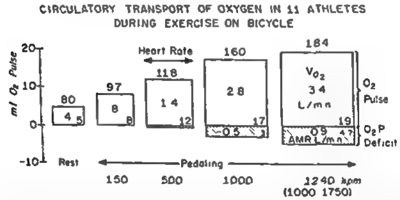

Fig 3 Serial changes in heart rate oxygen pulse and oxygen intake in L /minute in 11 physically active men who exercised on the bicycle ergometer for 5 minute periods without interruption and with increasing work loads until exhausted The final work load ranged from 1 000 to 1 750 kpm Note the progressive rise in anaerobic response to exertion under these conditions Notation for oxygen intake and oxygen pulse are the same as for Fig 2

the average responses in these 4 subjects revealed a much lower maximal ventilatory response on the bicycle (86 7 versus 137 4 L per minute) yet the maximal oxygen intakes were virtually identical (3 3 versus 3 4 L per minute) Thus the efficiency of respiration was substantially greater when the men were sitting on the bicycle rather than running upgrade on the treadmill Circulatory transport of oxygen essentially the same in terms of maximal heart rate and oxygen pulse But the relative supply of oxygen was lower on the treadmill because the anaerobic response averaged 40 rather than 18 per cent of the total metabolic activity. Since the latter was greater when the entire weight of the body had to be supported on the exercising legs the form of exercise influenced both the ventilatory and anaerobic

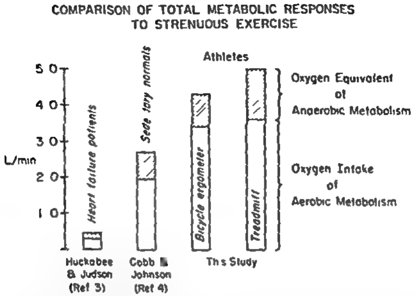

Fig. 4. Comparison of approximate levels of oxygen intake and anaerobic metabolism for strenuous exercise in patients in heart failure reported by Huckabee and Judson,[3] sedentary men reported by Cobb and Johnson,[4] and athletes in Groups II and III of this study. Despite these obvious differences, per cent responses of oxygen intake, which represent the aerobic contribution to total metabolic responses, were remarkably similar.

Discussion

Estimates of maximal intake of oxygen were consistent with those reported by Astrand,[9] Buskirk and co-workers,[10] and Mitchell and co-workers.[11] Whereas part of the greater variance may be methodological, it is important to emphasize that none of the subjects was studied in either the basal state or after repeated trials of exercise testing before definitive measurements were made. Under the conditions of arterial sampling, some experienced apprehension which could affect the ventilatory and possibly the circulatory responses to exertion. Finally, there were some differences in motivation to attain maximal exertion. This was apparent when a few subjects forced themselves to the point of collapse on the treadmill and became clinically ill with nausea, retching, and marked pallor immediately after exercise. Some were not fully recovered symptomatically until nearly an hour afterward.

Arterial sampling of concentrations of lactate and pyruvate at rest were obtained just prior to exercise and at the end of each period of exercise. Because some individuals were apprehensive about the unfamiliar experience of arterial cannulation as well as exercising and sampling under these conditions, the control values were not basal. Yet the magnitude of change which resulted from strenuous and maximal exercise overshadowed these minor deviations. The average concentrations of lactate immediately after exercise were in good agreement with those reported by Åstrand on more carefully selected subjects and under controlled experimental conditions.[9]

Even though large muscle masses are required to approach maximal energy expenditure, the type of exercise affects the physiologic responses. Holmgren and Strom[13] also concluded that the concentration of blood lactate was related to both the absolute physical work load and the individual's relative work with respect to physiologic responses. Despite similar levels of oxygen intake and heart rate, both ventilatory and anaerobic responses were substantially greater with the treadmill exercise which required the exercising legs to support all of the body weight. Just as whole body vibration at rest increases ventilation,[1] it is quite likely that running vigorously applies forces on the visceral organs impinging on the diaphragm which

may contribute to the exaggerated ventilatory response under these circumstances.*

Progressive increases in both absolute and relative levels of anaerobic metabolism with increasing severity of exertion clearly indicate that this response is not just characteristic of an individual's mechanisms of energy supply as implied by Huckabee and Judson[3] but is also markedly dependent upon the type and severity of the exercise stress. Accordingly, it is of interest to compare the relative contribution of anaerobic metabolism to the total metabolic responses of the patients in heart failure who were studied at low levels of exercise by Huckabee and Judson, the sedentary normal subjects submitted to prolonged strenuous exercise by Cobb and Johnson, and the athletes studied at maximal exercise in this study (Fig. 4). If marked differences in subjects and work loads are disregarded, there is a similarity of the per cent responses which suggests that acute circulatory insufficiency of oxygen transport might occur in any individual whenever the exercise stress approaches his maximal capacity. However, it is of major importance to note that the *absolute* levels of metabolic responses, both anaerobic and aerobic, for the four groups cited above are indeed quite different. For example, the total metabolic responses observed in the athletes running on the treadmill was ninefold greater than that reported by Huckabee and Judson for patients in heart failure. Similarly, the total responses of the sedentary men reported by Cobb and Johnson were intermediate between these two extremes. These observations lead to the conclusion that there are quantitative differences in circulatory capacity for oxygen transport between normal subjects and cardiac patients. Secondary differences in mechanisms of energy supply are dependent upon, rather than independent of, the severity and duration of exertion. Undoubtedly, the excellent studies of Huckabee and Judson would have revealed this had these investigators stressed normal subjects to their maximal capacity.

Transportation of oxygen by the circulation as defined by the Fick equation is the product of stroke volume and heart rate (or cardiac output) and arteriovenous oxygen difference.* The first two variables reflect the performance of the circulatory pump and the factors which modify it, whereas the last represents the average effectiveness of extraction of oxygen from the available flow of blood in all tissues. By substitution, oxygen pulse is also the product of stroke volume and arteriovenous oxygen difference. From earlier studies by Mitchell and associates[11] on normal men during maximal oxygen intake in the *upright* posture, neither stroke volume nor arteriovenous oxygen difference increased much more than twofold from rest to maximal exercise. Hence, the fourfold to fivefold increase in oxygen pulse observed in these studies approaches the limits which can be attained in normal subjects. Since these increments were inadequate for the actual energy requirements, acute circulatory insufficiency is considered to be the primary reason for the substantial anaerobic response observed under these conditions. Whereas acute circulatory insufficiency can occur in either normal subjects or cardiac patients in failure, the major difference is the fact that the cardiac patient† attains this limiting capacity for oxygen transport at very low work levels. With repeated stresses approaching maximal limits, various compensatory mechanisms for expansion of the extracellular fluid compartments, venous congestion and cardiac dilatation usually become evident.

Summary

1. Anaerobic responses to acute maximal exercise were studied in 32 physically trained men by serial changes in concentrations of blood lactate and pyruvate.

2. Excess lactate averaged from 7.9 to 10.7 mM per liter with different types of maximal exercise; accordingly, the estimated relative contribution of anaerobic metabolism to total metabolic responses ranged from 20 to 28 per cent.

*Alternatively, [illegible] might suggest that the relatively fixed position of the thorax in the subject working on a bicycle while sitting limits maximal ventilatory effort.

*Both the volume of blood and the characteristics of the oxygen dissociation curve are additional considerations.

†Then the oxygen pulse shows smaller increments with exertion primarily because of the limited stroke output of heart.

3 It was concluded that a major difference between normal subjects and patients in heart failure is primarily a quantitative difference in circulatory capacity for oxygen transport during exercise and any difference in mechanisms of energy supply secondary to this limitation of transport is also dependent upon the type severity and duration of exertion

Addendum

Attention is also directed toward the recent publications by Harris Bateman and Gloster[14] as well as by Olson[15] which criticize the basis for the derivation of excess lactate together with the correlation between changes in lactate pyruvate ratio (which are not utilized in Huckabee s equation) and changes in plasma volume with exercise as reported by Iseri and associates[16]

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On the duration of the isovolumetric relaxation period (IVRP) in dog and man

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The term "isovolumetric relaxation period" is probably more correctly substituted for the older expression "isometric relaxation period." The duration of this period has been evaluated by different methods. Its clinical importance is related to the fact that it is partly dependent upon the level of left atrial pressure and has been used as an index of left atrial pressure in cases of mitral stenosis. However, conflicting reports from several laboratories in regard to this relationship indicated a need for further study.

Material and method

I. Experimental study. The purpose of this investigation was to find the duration of the isovolumetric relaxation period (IVRP) of the left heart in the normal dog and to study its variations with different heart rates. The experiments were carried out in 13 adult mongrel dogs which weighed from 14 to 20 kilograms (average 18.9 Kg.). Anesthesia was obtained by subcutaneous injection of morphine sulfate (10 mg./Kg.) and intravenous injection of pentobarbital (25 mg./Kg.). One half of the initial dose of morphine was repeated every 2 to 3 hours. Additional doses of pentobarbital were given if necessary.

Left atrial and ventricular catheterizations were performed in all animals by the retrograde route, except in 4 animals in which the left atrium was entered by means of the transseptal approach. Equisensitive pressure systems with exact superimposition of base lines were employed. Statham P23Db gauges and 100 cm. long No. 10 catheters were used.

Pressure tracings, electrocardiograms, and phonocardiograms were simultaneously recorded by means of a Sanborn 8 channel recorder with photographic recording and a film speed of 200 mm. per second.

The isovolumetric relaxation period was measured from the initiation of the aortic component of the second sound to the point of crossing of the left atrial and ventricular pressures. The delay due to the pressure recording system was subtracted in the calculation of the IVRP.

II. Clinical study. This study aimed at ascertaining the normal range of IVRP in the right and left sides of the heart in man. The measurements were made on the records of the Laboratory of Cardiac Catheterization at Mount Sinai Hospital. Catheterization of the right side of the heart was performed via an antecubital vein in adults and via a saphenous vein

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Fig. 1. Measurement of the isovolumetric relaxation period (I.S.V.P.) (schematic). The two dotted lines indicate the incisura of the aortic pulse and the point of crossing of the left atrial and ventricular pulses.

in young children. Catheterization of the left side of the heart was performed using Björk's transthoracic approach as modified by Fisher from 1957 to 1961. Since then the transseptal method of Ross with a Brockenbrough needle has been used. In one case left ventricular pressure was recorded in a retrograde fashion through a femoral catheter. The aortic root pressure was always obtained by this retrograde method.

The isovolumetric relaxation period was measured in the intracardiac pressure tracings of 49 subjects without significant cardiovascular abnormalities. Nineteen of these tracings were excluded because details of the tracings were considered to be unreliable. Therefore, 30 cases were finally analyzed. This series included 14 males and 16 females aged from 3 to 43 years.

The pressure tracings were recorded only from the right side of the heart in 16 subjects. The other 14 subjects (except one) underwent simultaneous catheterizations of the right and left sides of the heart. 5 of these cases, however, were used only for the study of pressures in the left side of the heart.

The pressure tracings were recorded by either a Sanborn or an Electronics for Medicine multichannel photographic recorder using No. 8 cardiac catheters and Statham P23Db strain gauges. The paper speed was 50 mm. per second in 19 cases and 100 mm. per second in all others except 3 cases in which a speed of 200 mm. per second was used.

The tracings of right heart catheterization were studied by superimposing right atrial, right ventricular, and pulmonary arterial pressure curves recorded with a pullback maneuver. The position of the incisura of the pulmonary artery was also checked by comparison with the intravascular (pulmonary artery) phonocardiogram.* However, in 4 cases there was combined catheterization of the right and left sides of the heart with simultaneous right atrial and ventricular pressures and automatic superimposition. In tracings of left heart catheterization either three pressure tracings were simultaneously recorded or one pressure record obtained in a pullback maneuver was superimposed on the previously recorded two tracings. Superimposition of pressures was done only if the same preceding R-R interval and the same base line permitted exclusion of changes due to different rate or recording artefact. The cases which did not fit this criterion were excluded from the study, as mentioned above.

The subjects were classified as follows:

1. Ten subjects presented a systolic murmur which was subsequently explained as being caused by minor arterial abnormalities or was a flow murmur of the pulmonary artery or aorta. The murmur was recognized as being hemodynamically insignificant.

2. Eleven subjects had a probe patent foramen ovale or a probable small atrial or ventricular septal defect or patent ductus with no evidence of left-to-right shunt. A dynamically insignificant shunt was admitted.

3. Three subjects had a mitral murmur; however, left ventricular, left atrial, and

*Intracardiac and intravascular phonocardiograms were recorded according to the method described by Luisada and Liu. Since this method is based on differentiation and filtration of the electrical output of the strain gauge, no significant delay exists between intracardiac phonocardiographic waves and pressure waves.

right ventricular systolic and diastolic pressures were normal the pressure patterns were normal and there was less than a 1 mm gradient between the left atrium and the left ventricle A dynamically insignificant mitral lesion was admitted

4 Two subjects had a minimal aortic insufficiency

5 One subject was suspected of having myocarditis but the clinical picture was not severe and there was no hemodynamic evidence of heart failure

5 One patient had clinical evidence of coronary insufficiency but no hemodynamic evidence of heart failure

The measurements were made as follows (a) For the right heart from the nadir of the incisura of the pulmonary arterial pressure pulse to the point of crossing of the right atrial and right ventricular pressure pulses (b) For the left heart from the nadir of the incisura of the central aortic pulse to the point of crossing of the left atrial and left ventricular pressure pulses

Results

The data obtained in dogs are presented in Table I The average IVRP for the left heart was from 37 msec (rate 180 150 per minute) to 74 3 (rate 106 86 per minute) and to 60 6 (rate 56 54 per minute) In one animal marked changes in heart rate were observed In this particular animal the changes of the isovolumetric relaxation period of the left heart followed the general trend revealed by the Table In the other dogs the rate was stable but there were marked differences between animals due partly to individual variations and partly to a different reaction to the anesthetic For this reason a correlation was made between the isovolumetric relaxation period and the heart rate (R R interval) It can be seen from Table I that the IVRP increases when passing from severe tachycardia to a medium rate (106 86 per minute) Below this medium rate which seems to be optimal for the heart the correlation is less conclusive even though there seems to be a trend toward a decrease in such period in marked bradycardia

The data obtained in human subjects are presented in Table II The IVRP of the right heart ranged from 0 030 to 0 115 sec, with an average of 0 0492 sec that of the left heart ranged from 0 055 to 0 120 sec with an average of 0 0816 sec

In 9 cases in which measurement could be made on both sides of the heart the IVRP of the left ventricle was longer than that of the right ventricle in 7 cases by 0 038 to 0 065 sec (average = 0 042 sec) whereas in the other 2 cases the IVRP in the right heart was longer than that in the left heart by 0 025 and 0 050 sec respectively The end of the IVRP measured from the Q wave of electrocardiogram occurred earlier on the right side in 3 cases earlier on the left side in 4 cases and was simultaneous in 2 However the time difference was less than 0 02 sec in 6 cases in 2 cases the IVRP of the left heart was longer by 0 03 and 0 04 sec respectively and in 1 case the IVRP of the right heart was longer by 0 08 sec Including these 3 cases there was no significant average difference in timing of the end of the IVRP between the two sides of the heart

As shown by Table II there was no definite difference in the duration of the IVRP between the various age groups

No particular correlation was found between the IVRP and the heart rate partly because the range of rates was rather limited

Comments

The duration of the isovolumetric relaxation period (IVRP) has notable importance because were it possible to measure it by means of nontraumatic procedures it would permit evaluation of the level of pressure in the atria particularly that of the left atrium

According to Wiggers the IVRP averages 0 05 sec in dogs and 0 08 sec in man if both have a heart rate of 75 per minute

Since the report of Margolies and Wolferth[3] on the mitral opening snap the interval between the aortic component of the second sound and the mitral snap was considered to be equivalent to the IVRP of the left heart and a fairly close correlation was found between this interval and the level of left atrial pressure measured on catheterization[4,5] Unfortunately the opening snap does not accurately measure the time of opening of the mitral valve Moreover the absence of an opening prevents us from measuring the

interval in normal subjects and in many nonmitral patients

An attempt to measure this interval by electrokymography was made by Luisada and associates[13] In a recent study Legler and associates[14] attempted to measure such an interval by means of the phonocardiogram and the apexcardiogram The duration of the interval between the second sound and the 0 point of the apex cardiogram in 40 normal subjects averaged 0 06 sec (maximum = 0 09 minimum = 0 02)

Table I Isovolumetric relaxation of the left heart in dogs (in milliseconds)

Rate	180 150/min	150 120/min	120 106/min	106 86/min	86 76/min	76 66/min	66 56/min	56 54/min	Below 54/min
R R interval	301 400	401 500	501 600	601 700	701 800	801 900	901 1 000	1 001 1 100	1 101 1 200 or over
Average	37	59 8	60	74 3	66	58 3	59 5	60 [illegible]	64 3
Maximum	39	63	69	102	97	61	71	68	78
Minimum	35	57	50	49	50	54	52	57	61

Table II

Serial number	Age	Sex	Isovolumetric relaxation (sec) Left heart	Isovolumetric relaxation (sec) Right heart	Heart rate
1	3	M	——	0 050	115
2	3	F	——	0 045	96
3	4	F	——	0 100	104
4	5	F	——	0 060	127
5	6	M	——	0 040	80
6	6	M	——	0 030	127
7	7	M	——	0 030	95
8	9	M	——	0 030	78
9	10	M	0 060	0 110	108
10	10	F	——	0 035	135
11	10	F	——	0 035	100
12	11	F	——	0 030	100
13	13	F	0 115	0 050	122
14	14	F	——	0 040	68
15	14	F	0 065	0 035	69
16	15	M	0 055	——	80
17	16	M	0 055	0 080	79
18	16	F	——	0 030	75
19	16	M	0 090	0 040	58
20	17	F	——	0 040	75
21	18	M	——	0 035	71
22	22	F	0 080	——	67
23	25	M	0 120	——	57
24	25	F	0 090	0 030	75
25	26	M	——	0 075	76
26	32	F	0 080	0 030	85
27	37	M	0 085	0 035	91
28	35	M	0 090	0 115	86
29	43	F	0 065	——	78
30	43	F	0 105	——	76
	Average		0 0816	0 0497	
	Maximum		0 120	0 115	
	Minimum		0 055	0 035	

A study by Braunwald and associates[15] reported measurement of this interval by direct puncture of the heart in 3 cases (open chest) prior to lobectomy for pulmonary disease. Their data are 0.05, 0.08, and 0.11 sec.

One problem which puzzled many observers in the last decade was the following: If the *normal* IVRP of the left heart is about 0.07-0.08 sec, as previously stated, why does such an interval occasionally become 0.10-0.12 sec in mitral patients after commissurotomy, and why is it often in the same range in patients with minimal stenosis of the mitral valve or pure mitral insufficiency?

One possibility that should be considered is that such an interval has as a starting point the closure of the aortic valve. Phonocardiographic and other clinical measurements which take the second sound as a starting point may err by several milliseconds because the aortic component of the second sound is not simultaneous with valvular closure but *follows* it.[2, 16, 17] The studies of Mori[16] and MacCanon[17] from this laboratory demonstrated that closure of the aortic valve occurs first and is followed after 9 to 20 msec by the aortic component of the second sound. The latter again falls from 7 msec before to 13 msec after the aortic incisura. These data give the possible range of error which can be compounded by taking either the sound or the incisura as evidence of valvular closure. However, were this the cause of error, previous observations would contain an isovolumetric period systematically shortened (such a factor may be involved in the measurements of Legler and associates). On the other hand, Di Bartolo and associates[1] showed that the opening snap *follows* mitral opening. This is a factor which could lead to overestimation of the IVRP. Another possibility, which so far has not been admitted, is that the normal IVRP is *longer* than that previously considered. The present study in normal man revealed an *average* duration of 81 msec but also showed that in 3 subjects, ages 13 to 45 (Cases 21, 37, 46), the intervals were 105, 115, and 120 msec, respectively. This confirms Braunwald's finding (1 case out of 3) of an interval of 110 msec. Therefore, patients with minimal mitral stenosis and an interval between 110 and 120 msec *do not* have a prolongation because their interval is still within the upper limits of normal.

The IVRP of the right heart is much shorter than that of the left (average 49 vs. 81 msec). However, since the pulmonary incisura follows the aortic incisura by 30 to 40 msec, the opening of the tricuspid valve was approximately simultaneous with that of the mitral valve in several normal subjects. Exceptions can be found because Case 16 had a delayed opening of the tricuspid valve, whereas cases 21, 38, and 40 had a delayed opening of the mitral valve.

Therefore, in cases in which one finds an opening snap without knowing in which side of the heart it originates, one cannot interpret it on the basis of timing alone.

Summary

The isovolumetric relaxation period (IVRP) was studied in 13 normal anesthetized dogs and in 30 human subjects without hemodynamically significant abnormalities.

In dogs, this period was measured for the left heart from the aortic component of the second sound to the crossing of left atrial and ventricular pressure curves. A correlation between this period and the heart rate was made.

In human subjects, this period was measured on catheterization of the right side of the heart in 14 cases, on catheterization of the left side of the heart in 5 cases, and on catheterization of both the right and left sides in 9 cases. Measurements were made from the incisura of the pulmonary artery or aorta, respectively, and crossing of atrial and ventricular pressures of the respective side.

In dogs, the IVRP increased when passing from severe tachycardia to normal rate. On the contrary, a trend toward decrease was noted in bradycardia. The averages varied from 37 to 74.3 msec.

In human subjects, the IVRP of the left heart was longer than that of the right heart in 7 cases and shorter in 2 cases. No difference was found in the various age groups and no correlation with heart rate, possibly because the rates varied within a limited range.

In human subjects the average duration of the IVRP of the left heart was 81.6 msec with a maximum of 120 and a minimum of 55. For the right heart the average was 49.2, the maximum 115 and the minimum 35.

Even though the IVRP of the right heart is shorter than that of the left, pulmonary incisura follows aortic incisura. Thus the openings of the tricuspid and mitral valves may be simultaneous.

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Quantitative comparison of six nominally orthogonal vectorcardiographic systems

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It has been stated[1] that the number of systems of vectorcardiography in daily use is not much smaller than the number of cardiologists who occupy themselves with this branch of electrocardiography. Although this expression is obvious hyperbole, it serves to emphasize the currently unsatisfactory state of development in this field of cardiac electrophysiology. At present it appears unlikely that the ideal of a single theoretically accurate system equally applicable to all subjects in every circumstance can be attained. It is therefore the more imperative that the best systems available be thoroughly investigated to determine their interrelationships when applied to the same subject population.

Few such direct comparisons have so far been carried out using techniques which can claim satisfactory theoretical foundations. Langner and associates[2] studied the interchangeability of the systems of Schmitt and Simonson (SVEC III),[3] Frank,[4] McFee and Johnston,[5] and Helm,[6] but their method of assessment was such as to accentuate similarities and to minimize differences, since they paired the 3 leads of each orthogonal reference frame individually with a common lead to produce a loop. As a result of a somewhat subjective analysis they concluded that these four systems were interchangeable, "judged by present clinical standards," in all normal and the majority of abnormal subjects.

Pipberger and Lilienfield[7] compared the so-called "corrected" orthogonal systems of Schmitt and Simonson and of Frank with two that involve conventional bipolar and unipolar leads (Wilson's tetrahedron and Grishman's cube). They claimed that the two corrected systems, different in lead design, showed a very close relationship in their performance in man, but marked discrepancies occurred between the more conventional techniques. Subsequently Pipberger[8] stated that the systems proposed by McFee and Johnston, Schmitt and Simonson (SVEC III), Frank, and Helm all gave results in close agreement.

In 1959 Simonson, Schmitt, and Nakagawa,[9] in a comparison of eight vectorcardiographic lead systems in 4 subjects, cautioned against the too free interchange of results derived from the currently available nominally orthogonal lead systems. Large discrepancies were noted in the orientation and magnitude of mean and maximum QRS and T vectors and of the loop contour. In addition, vectorial respiratory shifts as recorded by the various techniques were large and mutually inconsistent.

A less satisfactory type of analysis has involved the comparison of the mean values obtained from the study of one group of subjects by a given lead system with the corresponding data from a second system applied to a different population. Such a

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study has been made by Bristow[10] who compared his own results using the Frank system with those of Pipberger using the SVEC III method and the data of Jordan and Beswick[11] obtained with a system based upon the lead field concept of McFee and Johnston. He demonstrated relatively minor differences between the first two methods, but that the last gave spatial QRS loops which were usually oriented more posteriorly and inferiorly. In contrast, Forkner, Hugenholtz, and Levine[12] commenting on the findings of several authors investigating separate populations concluded that whereas good agreement exists between the Frank and SVEC III systems in the frontal plane projections of the spatial vector, sagittal and horizontal plane projections diverge considerably.

An interesting experimental approach involving the insertion of an artificial dipole into the human cadaver was described by Burch, Cronvich, and Zao[13] who, in spite of considerable technical difficulty, were able to show that the Frank and SVEC III procedures gave results in reasonable agreement.

The only attempts which have previously been made quantitatively to relate pairs of vectorcardiographic systems were those of Burger, van Milaan, and Klip[14] and Burger, van Brummelen, and van Herpen.[15,16] They sought to derive linear expressions to allow of transformation between the results of several systems, including those of Schmitt and Simonson,[8] McFee and Parungao,[17] and Frank,[4] in order that investigators could continue to use the systems which they prefer but in order that the results would become generally comparable. When applied to single individuals the transformations were reasonably successful, but for large populations the average transformation showed a much wider scatter, which they interpreted as indicating that a linear expression is not a satisfactory description of the interrelationship between any two systems.

The primary purpose of the present investigation was to compare quantitatively on the same group of subjects the results given by the two nominally orthogonal lead systems developed in this laboratory in order to determine the degree of interchangeability between a technique involving the use of multiple electrode grids for the Y lead and one which differed only in that the grids were replaced by a pair of large metal discs. Secondarily, the results from these two methods were to be com-

Table I. Mean lead scalar area magnitudes (in microvolt seconds) for QRS and T as determined

	Lead X						Lead Y	
	Multiple electrode grid technique	*Large disc modification*	*McFee*	*Frank*	*Dower and Osborne*	*SVEC III*	*Multiple electrode grid technique*	*Large disc modification*
QRS								
Mean	10.0	11.0	12.0	13.5	10.0	8.5	20.0	20.5
S.D.	5.1	5.6	6.4	6.4	7.2	7.7	9.9	10.0
Coefficient of variation (percent)	51	51	53	47	72	91	50	49
T								
Mean	26.5	26.0	33.0	25.5	24.5	25.5	36.5	36.5
S.D.	12.1	11.5	14.8	11.3	9.7	20.[illegible]	13.6	13.9
Coefficient of variation (per cent)	46	44	45	44	40	81	37	38
Ratio means T/QRS	2.65	2.36	2.75	1.89	2.45	3.00	1.83	1.78

pared with those obtained by means of four other currently used techniques of vectorcardiography and at the same time the opportunity was to be taken of making detailed comparisons between the six methods in all combinations of pairs to establish their levels of correlation and interconversion

Methods

Sixteen clinically normal male medical students were the subjects of this investigation Each was examined successively by the following six vectorcardiographic techniques our multiple electrode grid Z lead method[11] our disc Z lead modification[11] McFee and Parungao s[17] Frank s[4] Dower and Osborne s[19] and Schmitt and Simonson s (SVEC III)[8] It may be pointed out that whereas the same X lead electrode placements are used in the first two of these methods all the remainder have individually different electrode positions for this lead Lead Y in all except Frank s and Dower and Osborne s systems is fundamentally the same although an amplifier calibration factor of 0 71 is imposed in SVEC III whereas the Z lead employed is different in each case With the subject lying supine the above mentioned order of procedure was found to give least disturbance to the individual and minimized the difficulty of changing electrode placements and recalibrating amplifiers

Scalar tracings from the X Y and Z leads for each system were recorded synchronously on a 4 channel Elema Mingograph 42 direct writing electrocardiograph at a paper speed of 100 mm per second Frontal horizontal and right sagittal planar loops were photographed on Kodak R 60 film from the screen of a Sanborn Vectorscope whose lead selector switch had been modified to permit the input of 3 independent bipolar leads The electron beam was interrupted every 0 0025 second and the direction of inscription was indicated by the blunt ends of the tear shaped light spots

The methods used for vectorial analysis of results and the symbols employed for presentation of the data are as previously described[11, 8] except that the lead nomenclature has been changed to conform with the conventional labeling of 3 dimensional Cartesian coordinates[18]

Results

Scalar lead magnitude values In Table I are presented for all six vectorcardio

by 6 vectorcardiographic techniques applied to 16 normal subjects

Lead Y—continued				*Lead Z*					
McFee	*Frank*	*Dower and Osborne*	*SVEC III*	*Multiple electrode grid technique*	*Large disc modification*	*McFee*	*Frank*	*Dower and Osborne*	*SVEC III*
21 0 10 6	16 0 7 3	8 0 4 1	14 5 7 0	−28 5 15 8	−20 0 11 1	−14 0 7 3	−9 0 5 9	−7 5 8 6	−7 0 4 7
51	46	51	48	55	56	52	66	115	67
39 0 16 [illegible]	25 [illegible] 10 4	3 5 3 7	27 5 10 7	67 5 26 4	54 0 18 2	36 5 16 7	29 5 10 9	34 0 11 1	27 0 12 0
43	41	106	39	39	34	63	37	33	44
1 86	1 59	[illegible] 44	1 90	[illegible] 37	2 [illegible]0	1 89	3 28	4 53	3 86

graphic methods the mean scalar area magnitudes (in microvolt seconds) for QRS and T in each lead as derived by algebraic summation of the areas enclosed by these deflections

For lead X QRS by Frank's method gave the largest area value (13 5 mvs SD 6 4) and SVEC III the smallest (8 5 mvs SD 7 7) but in contrast the former system manifested the closest grouping of individual observations around the mean as evidenced by the coefficient of variation (47 per cent) whereas the latter method showed the largest scatter with a coefficient of variation of 91 per cent For T McFee's technique gave the largest magnitude (33 0 mvs SD 14 8) the remainder of the methods yielding results approximately 15 per cent smaller but again the scatter was largest for the SVEC III system (C V 81 per cent)

In lead Y the most striking feature was the disparate nature of the results given by the Dower and Osborne method especially for T where the mean observed area magnitude was some 12 per cent of those derived by the Frank and SVEC III systems and only about 9 per cent of the remainder In addition the individual values for T were excessively widely scattered with a coefficient of variation of 106 per cent

As might be expected the mean scalar magnitudes for the Z lead demonstrated the greatest variability between the various methods The QRS value ranged from 28 5 mvs for the multiple electrode grid technique to 7 0 mvs for SVEC III and for T

Table II Statistical analysis of the differences between the lead scalar area magnitude means

Lead		Disc electrode—Multiple electrode	Disc electrode—McFee	Disc electrode—Frank	Disc electrode—SVEC III	Disc electrode—Dower	Multiple electrode—McFee
X	QRS						
	Mean difference	1 0	0 5	2 5	2 5	1 5	1 5
	S D	2 1	4 9	3 3	9 3	3 5	4 5
	Significance	−	−	+	−	−	−
	T						
	Mean difference	0 5	7 0	0 5	0 5	1 0	6 5
	S D	5 1	10 0	5 8	14 1	7 0	11 8
	Significance	−	+	−	−	−	±
Y	QRS						
	Mean difference	0 5	0 5	5 0	6 0	12 5	1 0
	S D	1 5	2 1	3 3	3 5	8 1	1 9
	Significance	−	−	++	++	++	−
	T						
	Mean difference	0 5	3 0	11 5	9 0	33 0	3 0
	S D	5 6	10 7	6 9	7 7	10 9	7 4
	Significance	−	−	++	+	++	−
Z	QRS						
	Mean difference	8 5	6 0	11 0	13 0	12 5	14 5
	S D	6 6	6 2	8 5	8 2	11 6	10 7
	Significance	++	+	++	++	+	++
	T						
	Mean difference	13 5	27 5	24 0	26 5	20 5	41 0
	S D	16 3	16 7	15 0	10 4	16 8	22 3
	Significance	+	++	++	++	+	++

Level of significance − indicates $p > 0.05$ ± indicates $p = 0.05 - 0.0$ + indicates $p < 0.02$ ++ indicates $p << 0.01$ $t > 5.0$

from 67 [illegible] mvs for the grid system down to 26 5 mvs for that of McFee

In order to establish for each lead the statistical significances of the differences between the scalar area magnitudes as determined by the six techniques the means of the 16 observed individual differences each estimated to the nearest 0 5 mvs have been utilized in preference to the differences between the gross means (as presented in Table I) The results of this statistical analysis are set out in Table II from which it is apparent that for both QRS and T in lead X most systems showed remarkably small differences between scalar areas the only significant disagreement for QRS being between the mean of Frank s system on the one hand and the comparable values for the large disc electrode the multiple electrode grid and the Dower Osborne techniques on the other In the case of T however the discrepant method appeared to be that of McFee which showed significant differences from the disc and Dower Osborne values and also possibly from those of the multiple electrode grid and Frank

In contrast there was little agreement between the means for lead Y among most of the pairs of methods only the disc multiple electrode grid and McFee techniques yielding statistically the same values for both QRS and T respectively Frank s method and that for SVEC III agreed only in the case of T

Similarly there was striking absence of agreement between the six systems as far as the Z lead was concerned only the

for QRS and T in all pairs of vectorcardiographic techniques

Multiple electrode—Frank	*Multiple electrode—SVEC III*	*Multiple electrode—Dower*	*McFee—Frank*	*McFee—SVEC III*	*McFee—Dower*	*Frank—SVEC III*	*Frank—Dower*	*SVEC III—Dower*
3 5 3 3 +	1 5 8 9 –	0 5 4 6 –	2 0 4 0 –	3 5 8 3 –	2 5 5 1 –	5 0 9 3 –	4 0 4 4 +	2 0 10 6 –
1 0 5 0 –	1 0 16 0 –	1 5 7 8 –	7 5 12 4 ±	7 5 18 9 –	9 0 10 0 +	0 0 15 8 –	1 0 5 9 –	1 0 16 2 –
4 5 2 9 ++	5 5 3 2 ++	12 5 8 3 ++	5 5 3 9 ++	6 5 4 2 ++	13 0 8 9 ++	1 5 0 9 ++	8 5 5 4 ++	7 0 5 0 ++
11 0 6 4 ++	9 0 6 5 ++	32 5 11 5 ++	14 0 8 0 ++	11 5 8 8 ++	35 5 13 6 ++	2 0 4 7 –	22 0 8 0 ++	23 5 8 4 ++
19 0 4 0 ++	21 0 12 9 ++	21 5 14 5 ++	5 0 6 0 +	7 0 4 5 ++	7 0 9 7 ±	2 0 3 3 ±	1 0 5 7 –	0 5 6 6 –
[illegible] 0 22 3 ++	40 5 19 2 ++	33 0 18 8 ++	3 0 [illegible] 3 –	0 5 14 0 –	7 5 14 6 –	2 5 8 7 –	4 0 11 0 –	7 0 11 3 –

Dower-Osborne method being indistinguishable from Frank and SVEC III for both QRS and T whereas McFee, Frank, SVEC III, and Dower-Osborne agreed in respect of T only.

Whether for any pair of methods the means differ significantly, it is possible for the pairs of individual values to be statistically correlated. Consequently, the correlation coefficients for both QRS and T area magnitudes in each of the 3 leads for all pairs of systems have been calculated together with their levels of significance and these data are presented in Table III.

The only system which for QRS failed to correlate with any of the others in lead X was Schmitt's SVEC III, although its mean did not differ significantly from that of any other method. For T, SVEC III correlated better with the remainder except in the combination with McFee.

For QRS in lead Y, all systems were remarkably well correlated despite the fact that only three pairs of methods gave differences between means which were not statistically significant. A generally similar situation existed for T, with the exception of those pairs involving the Dower-Osborne technique. This method was also less well correlated with the remaining five systems in lead Z.

Where corresponding leads from pairs of systems were shown to be correlated, the regression equations ($y = a + bx$) were calculated, the constants of which are set out in Table IV. From the value of $a \pm 2$ S.D. it is obviously possible to determine whether the regression line passes through the origin, and from [illegible] $\pm$ 2 S.D. whether the results are related by a slope of unity. If these two criteria are satisfied by corresponding leads of any two techniques, they can be regarded as directly interchangeable, as is observed by the coincident results obtained for QRS and T in leads X and Y for the disc electrode and multiple electrode grid methods wherein, in fact, the electrode placements for the derivation

Table III. Significance of the correlation coefficients calculated from the 16 individual values techniques

Lead		Disc electrode—Multiple electrode	Disc electrode—McFee	Disc electrode—Frank	Disc electrode—SVEC III	Disc electrode—Dower	Multiple electrode—McFee
X	QRS						
	r	+0.93	+0.68	+0.85	+0.03	+0.84	+0.71
	Significance	++	+	++	–	++	+
	T						
	r	+0.91	+0.73	+0.87	+0.[illegible]	+0.73	+0.63
	Significance	++	+	++	+	+	+
Y	QRS						
	r	+0.99	+0.98	+0.97	+0.98	+0.74	+0.9[illegible]
	Significance	++	++	++	++	+	++
	T						
	r	+0.92	+0.86	+0.88	+0.84	+0.53	+0.90
	Significance	++	++	++	++	–	++
Z	QRS						
	r	+0.95	+0.82	+0.61	+0.75	+0.41	+0.[illegible]
	Significance	++	++	+	+	–	++
	T						
	r	+0.79	+0.55	+0.57	+0.84	+0.45	+0.55
	Significance	+	±	±	++	–	±

Levels of significance: – indicates $p > 0.05$; ± indicates $p = 0.05 - 0.0$[illegible]; + indicates $p < 0.02$; ++ indicates $p << 0.01$ [illegible]

of these leads are respectively identical

Planar and spatial vectorial values Since the majority of previous comparative analyses of vectorcardiographic methods have utilized planar rather than scalar data planar angular values are presented in Table V to correspond with the mean scalar area magnitudes from the individual leads shown in Table I In addition the mean spatial QRS-T angle [(SP)$\hat{A}_{QRS-T}$] and spatial vectorial magnitudes [(SP)A] for QRS T and ventricular gradient (G) have been calculated

A statistical analysis comparable to that given in Table II but involving the vectorial data for all fifteen pairs of systems has been completed and the results are summarized in Table VI

In the frontal plane the Dower Osborne and Frank techniques gave angular values for QRS (42 and 49 degrees respectively) which were considerably smaller (i e the vectors were directed more horizontally) than the corresponding values as given by the other four systems which were among themselves statistically identical The same general relationships were manifest for T except that the Dower Osborne value (7 degrees) was approximately 40 degrees less than any comparable angle and therefore the frontal plane QRS T angle derived with these authors system is by far the greatest at 35 degrees

It is to be expected that because of the participation of the controversial *Z* lead (see Tables I and II) there will be little agreement between the angular values as calculated from the various systems for the horizontal and sagittal planes The only pair which showed good agreement for QRS and T in both planes was that involving Frank s and the SVEC III systems

Both modifications of our technique yielded larger spatial QRS-T angles than any other method except possibly Dower and Osborne s This is due to the more posterior location of the QRS vector together with a more anterior position of the T

for QRS and T lead scalar area magnitudes respectively for all pairs of vectorcardiographic

Multiple electrode—Frank	*Multiple electrode—SVEC III*	*Multiple electrode—Dower*	*McFee—Frank*	*McFee—SVEC III*	*McFee—Dower*	*Frank—SVEC III*	*Frank—Dower*	*SVEC III—Dower*
+0 86 ++	+0 08 −	+0 71 +	+0 79 +	+0 32 −	+0 70 +	+0 13 −	+0 78 +	−0 08 −
+0 82 ++	+0 64 +	+0 73 +	+0 58 +	+0 47 −	+0 68 +	+0 65 +	+0 83 +	+0 59 ±
+0 99 ++	+0 99 ++	+0 74 +	+0 97 ++	+0 97 ++	+0 73 +	+0 99 ++	+0 74 +	+0 74 +
+0 89 ++	+0 89 ++	+0 47 −	+0 92 ++	+0 87 ++	+0 19 −	+0 90 ++	+0 38 −	+0 60 +
+0 68 +	+0 [illegible] ++	+0 60 ±	+0 60 +	+0 80 +	+0 29 −	+0 82 ++	+0 80 +	+0 65 +
+0 56 ±	+0 75 +	+0 65 +	+0 80 ++	+0 57 ±	+0 54 −	+0 77 +	+0 53 −	+0 53 −

Since the Z lead value is also involved in the determination of all spatial vector magnitude data, it follows that there will be wide variability among the values for $(SP)A_{QRS}$ and $(SP)A_T$. The largest magnitudes for both QRS and T were manifest by the multiple electrode grid technique (39 and 83 mvs, respectively) and the smallest by the Dower-Osborne method. Only SVEC III and Dower-Osborne gave spatial vector magnitudes which did not differ statistically.

The spatial ventricular gradient, as defined by Ashman and Byer,[21] is obtained by vectorial addition of QRS and T, and consequently is dependent on the direction and magnitude of both components. Although in general the differences in ventricular gradient values reflected similar changes in T, it is possible, as shown by the pair multiple electrode and SVEC III, for there to be no difference between the spatial orientations of G, even though there may be between their magnitudes or, conversely, difference in orientation with constancy of magnitude, e.g., for the multiple electrode/McFee combination.

Typical sets of planar loops from 2 subjects are illustrated in Fig. 1 as recorded at the same levels of amplification. Apart

Table IV. Constants (and standard deviations) of the regression equations $y = a + bx$ relating leads

Lead			Disc electrode—Multiple electrode	Disc electrode—McFee	Disc electrode—Frank	Disc electrode—SVEC III	Disc electrode—Dower	Multiple electrode—McFee	Multiple electrode—Frank
X	QRS	a	+0.88 1.10	+4.09 2.00	+0.88 1.68		+3.61 1.26	+3.37 1.75	+0.66 1.51
		b	+1.008 0.109	+0.591 0.170	+0.715 0.123		+0.729 0.124	+0.572 0.150	+0.691 0.111
	T	a	+3.14 2.82	+7.39 4.68	+3.22 3.44	+15.24 2.48	+8.04 5.02	+9.42 5.53	+3.98 4.24
		b	+0.860 0.106	+0.564 0.143	+0.888 0.135	+0.420 0.098	+0.722 0.203	+0.520 0.169	+0.881 0.166
Y	QRS	a	+0.44 0.81	+0.91 1.08	−0.43 1.30	+0.30 1.16	+6.22 4.31	+1.77 2.02	−0.90 0.95
		b	+0.998 0.040	+0.931 0.051	+1.334 0.082	+1.404 0.080	+1.919 0.533	+0.871 0.095	+1.338 0.060
	T	a	+2.75 3.97	+8.58 4.53	+6.81 4.35	+6.87 5.22		+7.40 3.78	+6.52 4.02
		b	+0.934 0.109	+0.716 0.116	+1.176 0.171	+1.081 0.190		+0.737 0.096	+1.174 0.158
Z	QRS	a	−0.85 1.61	−2.23 3.28	−9.65 3.49	−7.55 2.87		−3.68 4.80	−12.20 4.58
		b	+0.668 0.057	+1.253 0.234	+1.142 0.394	+1.770 0.416		+1.760 0.344	+1.819 0.518
	T	a	+16.[illegible] 7.58			+19.31 6.00			
		b	+0.548 0.112			+1.273 0.221			

from confirming the general vectorial analysis described above, they provide a further basis for comparison by studying in detail the form of the inscribed loops to detect moment-to-moment characteristic features of outline. For example, in Subject No. 1 the multiple electrode grid, disc, McFee, and SVEC III all demonstrate similar anterosuperior terminal depolarization activity.

Discussion

The spatial vectorial approach to the investigation of cardiac electrical phenomena offers undoubted advantages as outlined by Pipberger[8] over conventional 12 lead electrocardiography, but these merits cannot be fully achieved until general agreement has been reached on the fundamental physical bases which govern the distribution of electrical phenomena throughout the body during the varying conditions of the cardiac cycle and until a system has been devised to measure accurately the corresponding instantaneous surface potentials.

In the present state of knowledge and absence of such agreement the benefits of vectorcardiography can probably best be realized by investigating in detail the rela

the individual values of lead scalar area magnitude for all correlated pairs of vectorcardiographic

Multiple electrode—SVEC III	Multiple electrode—Dower	McFee—Frank	McFee—SVEC III	McFee—Dower	Frank—SVEC III	Frank—Dower	SVEC III—Dower
	+4 34 1 72	+0 89 2 76		+4 67 2 18		+5 85 1 91	
	+0 563 0 169	+0 797 0 165		+0 694 0 214		+0 764 0 178	
+16 95 3 07	+5 11 5 96	+13 43 7 12		+10 25 , 68	+16 48 2 68	+3 71 4 46	
+0 375 0 121	+0 858 0 241	+0 758 0 287		+0 953 0 311	+0 357 0 110	+0 879 0 181	
−0 15 0 89	+6 01 4 26	−0 82 1 53	+0 01 1 45	+5 63 4 66	+0 72 0 48	+5 57 3 08	+4 87 2 90
+1 404 0 061	+1 912 0 527	+1 394 0 097	+1 463 0 100	+2 049 0 577	+1 041 0 033	+1 387 0 381	+1 321 0 359
+5 33 4 34		+1 64 4 15	+2 11 5 59		+1 45 3 10		
+1 174 0 157		+1 480 0 163	+1 346 0 202		+0 869 0 112		
−9 80 3 73		−7 52 2 30	−5 50 1 71		−1 67 1 52	−6 03 0 80	−4 56 1 00
+2 682 0 541		+0 731 0 261	+1 230 0 249		+1 041 0 191	+0 467 0 104	+0 367 0 130
+22 94 10 62	+15 15 17 19	−10 17 , 31			+12 07 4 57		
+1 643 0 393	+1 429 0 505	+1 234 0 216			+0 649 [illegible] 158		

Table V. Mean planar and spatial vectorial data derived from the 6 vectorcardiographic techniques

	Multiple electrode grid technique	*Large disc modification*	*McFee and Parungao*	*Frank*	*Dower and Osborne*	*SVEC III*
Planar value						
$F\hat{A}_{QRS}$	63	60°	61	49°	42	61
	13	13	16	15	22	14
$F\hat{A}_T$	54	55	51	46	[illegible]	54
	11	9	13	11	7	17
$F\hat{A}_{QRS\text{-}T}$	+9	+5	+10	+3	+35	+7
	15	16	16	17	24	14
$F\hat{A}$	58	58	54	47	20	56
	8	8	12	9	[illegible]	15
$H\hat{A}_{QRS}$	296	304	312	327	327	322
	22	23	22	26	36	31
$H\hat{A}_T$	68	65	41	50	53	53
	10	10	21	14	12	18
$H\hat{A}_{QRS\text{-}T}$	+132	+121	+89	+83	+86	+91
	30	29	36	34	45	43
$H\hat{A}_G$	39	41	13	27	38	35
	25	14	20	12	13	16
$S\hat{A}_{QRS}$	140	132	125	120	117	117
	23	23	20	24	40	23
$S\hat{A}_T$	29	35	56	40	[illegible]	45
	10	12	17	14	7	13
$S\hat{A}_{QRS\text{-}T}$	+111	+97	+69	+80	+111	+71
	28	28	31	33	43	29
$S\hat{A}_G$	61	60	80	64	26	65
	20	13	15	12	14	9
Spatial values						
$(SP)\hat{A}_{QRS\text{-}T}$	104	90	62	66	88	62
	28	27	27	30	43	28
$(SP)\hat{A}_{QRS}$	39 mv.s	33 mv.s	30 mv.s	25 mv.s	18 mv.s	20 mv.s
	13	10	10	[illegible]	6	8
$(SP)\hat{A}_T$	83 mv.s	72 mv.s	61 mv.s	49 mv.s	43 mv.s	49 mv.s
	27	20	20	14	12	21
$(SP)\hat{A}$	[illegible] mv.s	78 mv.s	79 mv.s	62 mv.s	47 mv.s	60 mv.s
	31	25	25	19	16	28

tive performances of the currently available techniques with the ultimate object of selecting the most nearly ideal method or more likely of achieving a most satisfactory compromise which, incidentally, will have to take account not only of purely theoretical factors but also of the technical practicability of its application in all circumstances of health and disease, habitus and posture, and possibly during exercise.

It was with these considerations in mind that we undertook the present study, first to ascertain to what extent simplification of the method originally developed in this laboratory influenced the recorded surface potentials and then to compare the results from this simplified technique with those obtained by four other nominally orthogonal vectorcardiographic lead systems. The simplification[18] achieved by substitution of a single thin fenestrated tin disc for each of the multiple electrode/resistor grids previously used for the Z lead had the dual advantages of extreme ease of actual manufacture of the discs and also of facility in their application to the thorax.

Since only the Z lead has been modified, it is obvious that all corresponding results involving exclusively leads X and Y, either

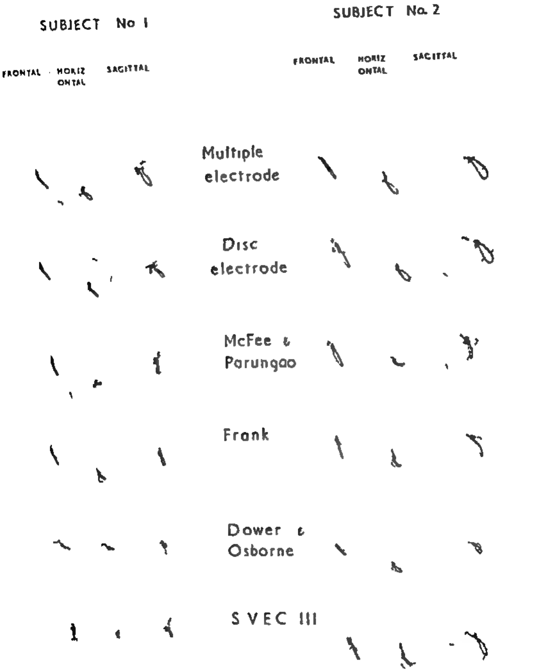

Fig 1 Representative planar loops for two typical subjects by six vectorcardiographic method

singly or in combination for the multiple electrode grid technique and its large disc modification should be identical and the fact that this is seen to be the case on reference to Tables I VI proves *inter alia* the validity of the experimental and analytical procedures employed in this investigation There was no significant difference between the mean scalar area magnitudes for QRS or T (Tables I and II) a highly significant level of correlation was demonstrated to exist between the two methods for all 16 individual subjects (Table III) and the calculated regression lines all passed through the origin and had slopes which did not differ *from unity (Table IV) In*

Table V Mean planar and spatial vectorial data derived from the 6 vectorcardiographic techniques

	Multiple electrode grid technique	Large disc modification	McFee and Parungao	Frank	Dower and Osborne	SVEC III
Planar values						
FA_{QRS}	63	60	61	49	42	61
	13	13	16	15	22	14
$F\hat{A}_{T}$	54	55	51	46	[illegible]	54*
	11	9	13	11	7	17
$F\hat{A}_{QRS-T}$	+9	+5	+10	+3	+35	+7
	15	16	16	17	24	14
$F\hat{A}_{G}$	58	58	54	4[illegible]	20	56
	8	8	12	9	9	15
HA_{QRS}	296	304	312	32	32[illegible]	322
	22	[illegible]3	22	26	36	31
HA_{T}	68	65	41	50	53	53°
	10	10	21	14	12	18
$H\hat{A}_{QRS-T}$	+132	+121	+89	+83	+86	+91
	30	29	36	34	45	43
$H\hat{A}_{G}$	39	41	13	27	38	35
	25	14	20	12	13	16
SA_{QR}	140	132	125	120	117	117
	23	23	20	24	40	23
$S\hat{A}_{T}$	29	35	56	40	6°	45
	10	12	17	14	7	13
$S\hat{A}_{QRS-T}$	+111	+97	+69	+80	+111	+71
	28	28	31	33	43	29
SA_{G}	61	60	80°	64	26	65
	20	13	15	12	14	9
Spatial values						
$(SI)\hat{A}_{QRS-T}$	104	90	62	66	[illegible]	62
	28	[illegible]	[illegible]7	30	43	28
$(SP)\lambda_{QRS}$	39 mv s	33 mv s	30 mv	25 mv s	18 mv s	20 mv s
	13	10	10	6	6	8
$(SP)\lambda_{T}$	83 mv s	72 mv s	61 mv s	49 mv s	43 mv s	49 mv s
	27	20	20	14	12	21
$(SP)A_{G}$	82 mv s	78 mv	79 mv s	62 mv s	47 mv s	60 mv
	31	25	25	19	16	28

tive performances of the currently available techniques with the ultimate object of selecting the most nearly ideal method or more likely of achieving a most satisfactory compromise which incidentally will have to take account not only of purely theoretical factors but also of the technical practicability of its application in all circumstances of health and disease habitus and posture and possibly during exercise

It was with these considerations in mind that we undertook the present study first to ascertain to what extent simplification of the method originally developed in this laboratory influenced the recorded surface potentials and then to compare the results from this simplified technique with those obtained by four other nominally orthogonal vectorcardiographic lead systems The simplification[18] achieved by substitution of a single thin fenestrated tin disc for each of the multiple electrode/resistor grids previously used for the Z lead had the dual advantages of extreme ease of actual manufacture of the discs and also of facility in their application to the thorax

Since only the Z lead has been modified it is obvious that all corresponding results involving exclusively leads X and Y either

system for lead X. However, the very high degree of scatter of the individual values was probably the reason that significant differences could not be demonstrated (Table II) nor any correlation be shown to exist between SVEC III and any other system for lead X scalar magnitudes.

The high coefficient of variation was also probably responsible for the apparent lack of statistical differences between the T mean values for this lead, but good correlation was observed between SVEC III, Frank's and the disc methods although they were not directly interchangeable.

For QRS there were also important differences in lead Y which characterized the SVEC III method, presumably due to its calibration factor. The mean area magnitude differed significantly from those derived from all other systems, although the corresponding individual observations were well correlated. The T mean area in this lead agreed only with that of Frank's method, but again there was good correlation between the SVEC III individual values and those of the other techniques except that of Dower and Osborne.

In lead Z the SVEC III mean values were similarly among the smallest in magnitude but differed significantly only from those of McFee and our disc modification. As before, there was, however, good individual correlation between this method and the others. For T there was good agreement in this lead between SVEC III and all the others except the disc technique.

In summary, therefore, it can be shown that Schmitt and Simonson's system registered in general smaller surface potentials, especially for QRS, in all 3 leads, and wide variability between observations from different subjects, with lack of complete interchangeability with other methods. This finding would supplement the previous observations of Simonson, Schmitt, and Nakagawa[4] that the SVEC III method was not freely interchangeable with several additional systems, and tends to oppose the view of Langner, Okada, Moore, and Fies that for practical purposes SVEC III is interchangeable with Frank's method, although the present results do suggest that the latter system showed fewer points of difference from SVEC III than any other of the techniques investigated.

Consideration of the performance of the

torcardiographic techniques

Multiple electrode—SVEC III	Multiple electrode—Dower	McFee—Frank	McFee—SVEC III	McFee—Dower	Frank—SVEC III	Frank—Dower	SVEC III—Dower
−	++	++	−	++	+	±	±
−	++	−	−	++	±	++	++
−	++	−	−	++	−	++	++
−	++	±	−	++	±	++	++
+	++	+	−	±	−	−	−
+	++	+	±	++	−	−	−
+	++	−	−	−	−	−	−
−	−	+	+	++	±	+	−
++	++	−	+	−	−	−	−
++	++	++	+	++	−	++	++
++	−	±	−	−	−	+	+
−	++	++	+	++	−	++	++
++	−	−	−	−	−	−	−
++	++	+	++	+	+	+	−
++	++	++	+	+	−	−	−
+	++	++	+	++	−	++	−

Frank technique in comparison with those of Dower and Osborne McFee and Parungao and our disc electrode shows that it disagreed in lead Y with all the others for both QRS and T mean scalar area magnitudes whereas in the remaining leads its comparative treatment of QRS and T in relation to the other methods was less consistent In lead X although the T values agreed with all other systems QRS agreed only with McFee and in lead Z the observed data for both QRS and T agreed only with Dower s system Despite this lack of complete agreement between mean values the individual values for QRS in all four of these systems could be mathematically interrelated since satisfactory correlation coefficients could be derived from all paired sets of data It is apparent therefore that although Dower and Osborne based their method essentially on that of Frank the practical simplification involving the reduction of electrode positions from 7 to 4 resulted in appreciable modification of lead response

The outstanding characteristic of the Dower and Osborne system was the insensitivity of the Y lead relative to those of the other techniques investigated particularly in respect to T so that for this lead the ratio of T to QRS scalar area was reduced to 0 44 compared with approximately 1 8 for the other methods and the frontal plane projection of T was raised nearly to the horizontal

From the point of view of voltages registered the McFee and Parungao system approximated most closely those of the disc method and consequently the planar loops obtained by these two lead systems were of generally most similar dimensions but the outstanding difference lay in the more vertical disposition of the T loop in the McFee records This is apparently due to the unequal attentuation of QRS and T voltages resulting in a ratio of T to QRS mean scalar areas of 1 9 which is substantially lower than for any other technique

In conclusion it may be emphasized that in order ultimately to decide on the most satisfactory compromise lead system to be adopted for universal application in vectorcardiography account should be taken not only of the quantitative mathematical comparisons but also of those characteristics which can be included under the term practicability Such features as least quantity complexity and cost of equipment its ease of calibration and immunity from extraneous electrical interference and simplicity of electrode application in adverse circumstances should also be considered Our subjective impressions are that the most practicable of these techniques is the large disc modification of our original method and that the sequence McFee and Parungao Dower and Osborne Frank and Schmitt and Simonson s SVEC III lists the other methods in order of increasing complexity

Summary

Each of 16 normal males was examined by two vectorcardiographic techniques previously described by us and also by the lead systems of Schmitt and Simonson (SVEC III) Frank Dower and Osborne and McFee and Parungao For each subject the scalar area magnitudes in leads X Y and Z and the planar and spatial vectorial values were determined by all six methods of vectorcardiography The corresponding means and the results of a statistical analysis comparing the performance of every technique with that of the others are presented

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The effects of norepinephrine on the hemodynamics and myocardial metabolism of normal human subjects

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Despite the widespread clinical use of norepinephrine as a vasopressor, the changes which it produces in the coronary circulation and myocardial metabolism are not well defined in human subjects. It is well known that infusion of norepinephrine in man results in increased myocardial work. In experimental animals various investigators have reported that there is also increased myocardial oxygen extraction, elevated coronary blood flow, and possibly glycolysis during infusion of norepinephrine.[1-4]

This study has been undertaken to investigate the changes in coronary blood flow, myocardial oxygenation, and myocardial substrate utilization that occur during infusion of norepinephrine in normal human beings.

Material and methods

Fifteen patients without cardiovascular or metabolic diseases were studied. All patients were postabsorptive and none had been given premedication. Pressures in the right atrium, right ventricle, pulmonary artery, and pulmonary wedge positions were obtained. Cardiogreen dye was injected into the right atrium and the dye dilution curve was recorded from the brachial artery.[5] The coronary sinus was then intubated and the coronary blood flow was determined by the N_2O desaturation method.[6] Simultaneous samples of arterial and coronary venous blood were obtained for determinations of oxygen and carbon dioxide,[7] lactate,[8] and pyruvate.[9] In 5 patients free fatty acids (FFA)[10] and glucose[11] were also determined. After these base line determinations had been made, 2 μg per milliliter of norepinephrine in normal saline was given by slow infusion into a peripheral vein until a consistently elevated arterial pressure of about 30 mm. Hg was obtained. The measurement of coronary blood flow and

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arteriovenous samplings were then repeated and the catheter was withdrawn into the right atrium. Cardiogreen was then again injected into the catheter.

Cardiac output was calculated from the indicator-dilution curves by the Stewart-Hamilton method.[12] Myocardial work was calculated as tension time index (TTI).[13] Myocardial oxygen consumption (QO_2) was obtained as the product of coronary blood flow and coronary A-V oxygen difference (Δ A-V O_2) and expressed as cubic centimeters per minute per 100 Gm. of left ventricle. Myocardial efficiency was determined as TTI/QO_2.[14] Coronary perfusion pressure was determined as the difference between mean brachial arterial and mean right atrial pressure. Coronary vascular resistance was calculated as coronary perfusion pressure/coronary blood flow expressed in millimeters of mercury per cubic centimeter per minute per 100 Gm. of heart muscle.[15]

The redox potential of the lactate-pyruvate system in the coronary venous and arterial blood was calculated from the formula

$$E_h = E_0 - \frac{RT}{nF} \ln \frac{Red}{Ox}$$

E_0 is the standard redox potential at pH 7 when the molar concentration of the oxidized substrate equals the molar concentration of the reduced form. The E_0 for the lactate-pyruvate system is -204 mV. at 37°. In this equation n represents the number of electrons transferred according to the chemical equation. F is the Faraday constant (23.068 cal/V. equiv.), R is the gas constant (1.987 cal/mole/degree), and T is the absolute temperature. Thus by substitution

$$E_h = -204 - 30.7 \log La/Py$$

It has been shown in this laboratory that changes in the difference in the redox potential as calculated from the ratio of lactate/pyruvate in coronary venous and arterial blood reflect changes in the oxidation-reduction potential of the lactate-pyruvate system of heart muscle itself.[16,17] This was demonstrated in experiments in which the oxidation-reduction (redox) potential of the heart muscle was obtained directly and compared with the difference in the redox potential (ΔE_h) between coronary venous and arterial blood. In myocardial anoxia ΔE_h becomes negative. In this study the difference in redox potential between coronary venous and arterial blood (ΔE_h) was used as index for the balance between the supply of oxygen to the heart and the myocardial demands for oxygen, henceforth referred to as oxygenation of the heart. The p values were calculated as described by Croxton.[18]

Results

The hemodynamic changes resulting from the infusion of norepinephrine are shown in Table I. There was an elevation of the mean brachial arterial pressure from 99 to 126 mm. Hg. The heart rate slowed from 73 to 65 beats per minute. Although most subjects had an increase in cardiac output, this finding was not consistent. Coronary blood flow did not change significantly except for Subjects 8 and 10 who showed a marked decrease after infusion of norepinephrine (Table I). Coronary vascular resistance increased in all but one subject (Table I). Myocardial oxygen consumption showed no significant change despite a marked increase in myocardial work (Table I). This resulted in a higher myocardial efficiency.

The metabolic changes resulting from the infusion of norepinephrine are shown in Table II. Myocardial oxygen extraction increased in 12 out of 15 subjects. The myocardial production of CO_2 increased. The most remarkable change in the myocardial substrate utilization was an increase of 252 per cent in extraction of FFA. No significant changes in myocardial extractions of glucose or lactate were noticeable. In most hearts the myocardial pyruvate balance became negative. The difference in redox potential between coronary venous and coronary arterial blood (ΔE_h) became positive during the infusion of norepinephrine.

Discussion

It has been reported that norepinephrine is essentially a coronary vasodilator;[19,20] however, Berne concluded that norepinephrine has a primary coronary vasoconstrictor action and that the vasodilator effect of this amine is probably the resul

Table I Hemodynamic findings before and after infusion of norepinephrine in 15 normal h iman subjects

Subject		Rate per minute	CI (l /min /M²)	B 1 mean (mm Hg)	CR (mm Hg/c c / 100 Gm LV/min)	CBF (c c /100 Gm LV/min)	TTI (mm Hg sec)	q O₂ (c c /100 Gm LV/min)	Eff (mm Hg sec / c c /100 Cm LV/min)
1	Before	75	3 55	100	—	—	—	—	—
	After	64	—	118	—	—	—	—	—
2	Before	66	4 38	78	1 19	62	1 841	6 07	303
	After	50	4 54	121	1 60	73	2 712	7 43	365
3	Before	88	4 61	102	0 8	124	3 643	9 6	379
	After	84	—	137	1 0	125	4 019	9 4	427
4	Before	66	2 4	97	1 ?	78	2 468	7 83	?66
	After	56	3 0	110	1 1	80	2 475	8 30	298
5	Before	81	2 78	110	—	—	2 988	—	—
	After	75	—	148	—	—	4 440	—	—
6	Before	56	3 66	84	1 14	69	1 999	7 45	268
	After	46	3 67	115	1 71	63	2 495	6 07	411
7	Before	86	4 68	[illegible]	1 33	60	2 641	7 30	361
	After	80	3 80	130	2 7	55	4 096	7 33	558
8	Before	66	3 39	88	0 83	102	2 356	9 42	250
	After	61	3 59	115	? 32	47	3 184	8 (0	370
9	Before	72	3 91	115	1 69	65	2 880	7 55	381
	After	80	3 65	128	1 86	66	3 379	8 20	412
10	Before	70	3 9	90	0 95	90	2 100	9 07	231
	After	56	4 3	118	1 70	63	2 352	7 03	334
11	Before	64	—	95	—	—	—	—	—
	After	60	—	107	—	—	—	—	—
12	Before	72	—	90	—	—	—	—	—
	After	65	—	105	—	—	—	—	—
13	Before	80	—	97	—	—	—	—	—
	After	69	—	106	—	—	—	—	—
14	Before	63	3 89	100	—	—	—	—	—
	After	58	4 01	117	—	—	—	—	—
15	Before	86	—	110	—	—	—	—	—
	After	66	—	130	—	—	—	—	—
Mean	Before	73	3 7	96	1 14	81	2 546	8 03	305
	After	65	3 8	120	1 7	71	3 239	7 90	397
		p < 005	p > 050	—	p > 005	p > [illegible]	p < 005	p < 100	p < 005

Table II Metabolic findings before and after infusion of norepinephrine in 15 normal human subjects (Δ refers to A V difference)

Subject		B 1 O_2 (vol %)	Δ O_2 (vol %)	B 1 CO_2 (vol %)	Δ CO_2 (vol %)	Lactate (mg %)		Pyruvate (mg %)		Glucose (mg %)		Fatty acids (μ mol /L)		RQ	Δ E_h (mV)
						B 1	Δ	B 1	Δ	B 1	Δ	BA	Δ		
1	Before	14 76	7 14	44 82	4 08	3 60	0 0	190	020	—	—	—	—	—	− 3 8
	After	14 66	7 39	47 15	4 20	5 22	9	180	007	—	—	—	—	—	+ 3 3
2	Before	14 29	9 8	—	—	6 70	1 59	266	085	—	—	—	—	—	− 1 5
	After	14 9	10 18	—	—	6 84	1 44	164	− 015	—	—	—	—	—	+ 4 1
3	Before	11 62	7 74	53 9	4 19	4 23	1 70	175	056	—	—	—	—	82	− 1 8
	After	11 50	7 50	53 38	5 47	4 00	2 12	109	− 015	—	—	—	—	73	+ 5 0
4	Before	11 87	10 04	48 23	6 64	4 47	24	294	035	—	—	—	—	66	+ 2 1
	After	11 87	10 34	45 97	8 30	5 11	97	122	065	—	—	—	—	60	+11 9
5	Before	16 21	11 97	45 10	7 98	4 54	1 08	248	026	—	—	—	—	73	− 1 5
	After	16 45	10 83	39 88	8 22	5 67	1 92	141	090	—	—	—	—	76	+ 5 2
6	Before	17 69	10 79	50 11	9 35	4 71	1 92	396	219	—	—	—	—	88	+ 7 1
	After	17 82	9 64	49 21	8 4	9 27	5 32	293	088	—	—	—	—	73	+ 9 0
7	Before	14 82	17 13	50 42	8 01	4 54	0 04	182	− 080	—		—	—	66	− 7 2
	After	16 12	13 37	49 24	8 77	4 59	0 72	141	− 113	—		—	—	65	+ 5 6
8	Before	13 51	9 24	40 07	7 39	3 18	0 30	171	− 000	—	—	—	—	78	− 6 5
	After	14 37	10 34	46 55	7 06	3 25	0 45	114	− 129	—	—	—	—	68	+10 1
9	Before	16 73	11 62	49 16	8 29	3 30	0 90	194	056	—	—	—	—	11	+ 5 3
	After	16 92	12 42	46 37	9 70	4 11	0 95	169	− 014	—	—	—	—	79	+ 8 4
10	Before	15 67	10 08	51 09	1 07	4 05	0 74	202	010	—	—	—	—	10	− 2
	After	15 91	11 16	47 08	7 94	4 42	0 45	182	− 059	—	—	—	—	71	+ 4 6
11	Before	12 24	9 6	48 16	6 65	10 47	3 55	589	028	79	10 2	036	029	77	− 3 8
	After	12 85	7 57	46 20	9 35	8 13	3 47	053	015	83 8	9 7	053	045	87	− 1 9
12	Before	13 91	11 43	48 06	8 17	4 49	0 15	297	− 014	93 2	4 51	093	050	72	+ 4 3
	After	13 97	12 31	48 96	7 56	5 49	2 0	261	− 03	98 2	3 18	097	087	61	+ 7 5
13	Before	14 20	9 51	47 50	9 59	5 59	2 27	635	210	72 78	44	030	015	1 0	+10 6
	After	15 16	10 6	48 08	1 44	4 38	2 26	117	− 065	79 32	6 54	015	037	10	+15 7
14	Before	14 36	9 13	51 85	6 32	8 04	4 25	220	− 041	—	—	033	008	69	+12 6
	After	15 17	10 44	48 51	8 10	5 41	4 72	07	− 073	—	—	07	047	78	+17 7
15	Before	13 84	10 66	46 06	8 07	9 17	2 78	539	196	95 58	4 1	06	022	76	+ 1 7
	After	14 15	10 91	45 01	8 22	6 64	2 22	371	103	100 71	2 14	159	097	75	+ 9
Mean	B	14 37	10 00	48 82	7 48	5 40	1 43	306	053	85 2	4 82	050	075	76	—
	A	14 78	10 47	46 90	7 70	5 77	1 99	176	− 008	90 5	5 26	085	063	74	—
p		> 100	> 100	< 010	< 100	< 100	< 100	< 010	< 005	> 100	> 025	< 005	< 005	> 100	

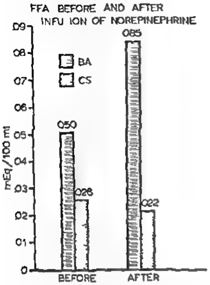

Fig. 1. Shows the concentration of FFA in blood in the brachial artery (*BA*) and coronary sinus (*CS*) before and after the infusion of norepinephrine.

of increased myocardial metabolism. Utilizing low perfusion pressure, he found an initial decrease followed by increase in coronary blood flow.[21] Using a high coronary perfusion pressure and well oxygenated blood, however, he found no increase in coronary blood flow after intracoronary infusion of norepinephrine. Similar results were reported by Marchetti and co-workers[2] and by Hardin and his associates. Masuda,[3] perfusing the left coronary artery under constant pressure in closed-chest dogs, concluded that norepinephrine has coronary vasoconstrictor action. Although it is not possible to determine instantaneous changes in coronary blood flow by the N_2O method, it has been proved to be satisfactory in measuring mean directional changes.[15, 23]

Our results indicate that norepinephrine has no coronary vasodilator effect in the normal human subject, since coronary vascular resistance increased. This may have been due either to constriction of the coronary arteries or to increased intramural pressure resulting from augmented force of contraction. The myocardial efficiency increased because of an elevation in myocardial work without corresponding elevation of the myocardial oxygen consumption. The increase in the tension-time index was the result of higher systemic arterial pressure and of longer ventricular ejection time (Fig. 1).

The action of norepinephrine on myocardial oxygenation continues to be controversial. Experimental evidence exists for both increased myocardial oxygenation and myocardial anoxia.[4, 6] In the present study, we have utilized the difference in the ratio of lactate/pyruvate between coronary venous and arterial blood (ΔE_h) as an index of myocardial oxygenation. Our results show a consistent change in ΔE_h to more positive values (Table II). This indicates increased oxygenation of the myocardium and casts doubt on the development of glycolysis in the heart muscle. It is understood that the changes in ΔE_h reflect only qualitative alterations in the redox potential of the lactate/pyruvate system of heart muscle; they do not represent the sum of the redox potentials of all the redox systems.

It has been demonstrated that catecholamines stimulate the release of FFA from fat depots[27, 28] and raise the level of the plasma FFA.[29, 31] It is known that after the injection of norepinephrine the rise in circulating FFA results in a marked increase in the myocardial extraction of the substrates.[31] In the present study, a rise of 167 per cent in the arterial level of FFA was observed during infusion of norepinephrine. This was associated with an increase *of 252 per cent in the myocardial extraction* of FFA (Fig. 2). The myocardial extraction of glucose decreased, which indicates that energy for the performance of increased myocardial work is probably derived from the catabolism of FFA.

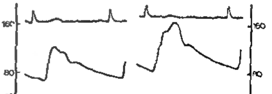

Fig. 2. Shows the electrocardiogram (Lead II) and the brachial arterial pressure tracing of a representative patient before and after the infusion of norepinephrine. Note the slower heart rate and prolonged ejection time after the infusion of norepinephrine.

The effect of increased myocardial utilization of FFA upon carbohydrate metabolism is expressed in decreased utilization of glucose and pyruvate and more positive values of ΔE_h. The FFA compete with pyruvate for the formation of acetyl coenzyme A; utilization of FFA is the favored process. Consequently, the pyruvate level increases, leading to its diminished uptake from the perfusing blood; furthermore, the breakdown of glucose through the Emden-Meyerhof pathway decreases. The FFA combustion results in a higher production of energy per mole of oxygen, and this then is a reasonable explanation for a seemingly better oxidative metabolism as expressed by the increasing positive values of ΔE_h.

Summary

Studies on the circulation and on cardiac metabolism were carried out during intravenous infusion of norepinephrine in 15 human subjects. There was a marked increase in the myocardial extraction of free fatty acids. No significant change in coronary blood flow or myocardial oxygen consumption was observed. Coronary vascular resistance and myocardial efficiency increased. A rise in the difference in the redox potential (lactate/pyruvate) between coronary venous and arterial blood (ΔE_h) was found during infusion of norepinephrine. This demonstrates increased oxygenation of the heart muscle under these conditions.

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Case reports

Measles myocarditis

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Although measles is a common and well studied disease which may involve several organ systems, often severely, cardiac involvement is a rarely reported complication.[1-7] This is particularly true if one considers only well-documented cases of myocarditis associated with measles. This is the report of a previously healthy adult with strong clinical and laboratory evidence of myocarditis associated with serologically confirmed measles.

Case report

A 29-year-old white man was admitted to the U.S.P.H.S. Hospital, Boston, Mass., on Jan. 12, 1962, because of fever and abdominal pain. He had been in good health until 4 days prior to admission, when he had had the gradual onset of rhinorrhea, nonproductive cough, sore throat, and generalized myalgia. Two days prior to admission he developed fever and chills. On the day before admission, redness and burning of the eyes occurred, accompanied by increased lacrimation. Also on that day the patient began to have abdominal pain with nausea and some vomiting, and he noted for the first time an erythematous rash on the face and neck. At this point a physician was consulted, who administered penicillin. However, the fever, weakness, and abdominal pain continued to increase and the patient came to the hospital.

The patient's medical history was unremarkable. He did not know whether he had had measles in childhood. Information obtained later revealed that the patient had been exposed to a neighbor's child with measles approximately 2 weeks prior to admission.

Physical examination on admission revealed a well-developed, muscular white man who was acutely and severely ill. He was pale and sweaty and complained of abdominal pain, nausea, mild dyspnea, inability to get comfortable, and weakness so severe that he could not sit up. The temperature on admission was 104.6 F., the pulse was 120 and weak, the blood pressure was 140/80 mm. Hg, and the respiratory rate was 32. There was no pulsus paradoxus. There was an obvious conjunctivitis bilaterally, with redness, yellow exudate, and photophobia. The eyes were otherwise normal. The pharynx was moderately diffusely injected, with no exudate. There were small white patches on the buccal mucosa which were not typical of Koplick's spots. There was no nuchal rigidity. The patient had tender posterior cervical adenopathy, with no abnormal lymph nodes elsewhere. The chest moved symmetrically with respirations. The lungs were clear. The heart sounds were distant, with a regular tachycardia. There was no pulse deficit. The quality of the sounds was poor, and there was no difference between the first and second sounds. There were no murmurs, nor was any rub heard. There was no gallop. Examination of the abdomen revealed no distention, nor was the liver or spleen palpable. There was mild tenderness in the right lower quadrant, without rebound or referral. The bowel sounds were normal. There was a maculopapular rash which was confluent on the face and more discrete behind the ears, on the neck, and on the trunk. The remainder of the physical examination revealed no abnormalities.

Laboratory data on admission showed a white blood cell count of 4,500, with 15 neutrophils, 65 band forms, 13 lymphocytes, and 1 eosinophil. The erythrocyte sedimentation rate was 19. The hematocrit was 50. Hemoglobin was 16 Gm. per cent. Examination of the blood smear showed several of the neutrophils to have toxic granules. Urinalysis was within normal limits. Serum lipase was 0.2 Sigma Tietz units, amylase 45 mg. per cent, SGOT 230 units, SGPT 300 units. Heterophile agglutination test was negative. There was no titer of cold agglutinins. Weil-Felix and Widal tests were negative. The antistreptolysin-O titer was less than 100 units per cubic centimeter. Sputum cultures and

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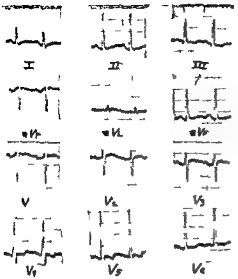

Fig. 1. Electrocardiogram on the day of admission.

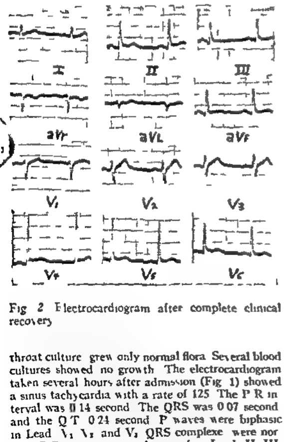

Fig. 2. Electrocardiogram after complete clinical recovery.

throat culture grew only normal flora. Several blood cultures showed no growth. The electrocardiogram taken several hours after admission (Fig. 1) showed a sinus tachycardia with a rate of 125. The P-R interval was [redacted] 14 second. The QRS was 0.07 second and the Q-T 0.24 second. P waves were biphasic in Leads V1, V2, and V3. QRS complexes were normal. S-T segments were depressed in Leads II, III, and aVF and were somewhat elevated in Lead V1 and V. There was upward coving of the S-T segments in Leads V1, V2, and V3. The T waves were inverted in Leads II, III, and in V4, V5, and V6. They were biphasic in Lead aVF and nearly flat in Lead aVL. This tracing was interpreted as showing S-T and T wave changes consistent with myocardial ischemia.

A chest x-ray film taken at the time of admission showed clear lung fields and normal size and configuration of the heart, with no evidence of pulmonary congestion. Serial chest x-ray films revealed no change, particularly in the size of the heart. Flat films of the abdomen taken on admission were normal.

On the second hospital day the bilirubin was 0.5 mg. per cent, thymol turbidity was 6.3 units, cephalin flocculation 3 plus, total protein 6.7 Gm. per cent, with an albumin of 4.0 and a globulin of 2.7. The alkaline phosphatase was 3.1 Bessey-Lowry units, the SGOT was 95 units, SGPT was 180 units, and the lactic acid dehydrogenase was 720 units. Prothrombin time showed [redacted] per cent activity. The Bromsulphalein retention was 12 per cent in 45 minutes.

Follow-up laboratory results are as follows: the white blood cell count rose to a high of 10,000 on the sixth hospital day, with a differential of 61 neutrophils, 2 metamyelocytes, 5 band forms, 19 lymphocytes, 11 monocytes, and two young lymphocytes. The sedimentation rate on that day was 43 (Wintrobe). Hematological abnormalities then gradually returned to normal. Repeat agglutination tests all showed no change. Repeat Bromsulphalein retention was 3 per cent in 45 minutes on the twelfth hospital day. Follow-up liver function tests and serum enzymes gradually returned to normal. Complement fixation tests for measles showed a titer of 1:2 on January 15, and a titer of greater than 1:128 on January 29.* Serial electrocardiograms gradually returned toward normal. It is notable, however, that there were still considerable S-T and T wave changes when the patient was virtually afebrile and when the cardiac rate was normal.

The patient was treated symptomatically and with supportive therapy, getting intravenous fluid, rest, salicylates, and sponging. His temperature continued to be elevated as high as 105° F. for the first 4 hospital days. During this time he continued to be markedly toxic. His extreme weakness, mild dyspnea, and heart sounds of poor quality continued. During this time the patient's color was quite poor, with his lips and nail beds being cyanotic and his pulse continuing to be weak.

During the initial hospital days the rash progressed to involve the extremities. At the end of the fourth hospital day the rash began to fade and become brown and scaly, and then disappeared progressively. At the same time the patient began gradual clinical recovery, with a decrease in fever, pulse rate, and weakness. The remainder of his hospital course was uneventful, being one of gradual recovery.

The patient was discharged at the end of 13 hospital days, at which time he felt generally well except for some mild residual weakness. On outpatient follow-up he returned to a state of perfect health and was able to resume working. Follow-up electrocardiograms showed reversion to normal (Fig. 2).

*Performed through the courtesy of Dr. Bruce D. ... Children's Hospital Medical Center, Boston, Mass.

The epilogue to this case report is the fact that the patient's three children and his sister all became ill with measles on Jan. 24, 1962.

Discussion

This case was one of serologically confirmed measles in an otherwise healthy man who made a complete recovery. The patient presented strong clinical evidence of cardiac involvement without any evidence of pericarditis. The extreme weakness, dyspnea, cyanosis, poor quality of the pulse, and metronomic cardiac rhythm are all consistent with the classic clinical descriptions of myocarditis. The electrocardiographic abnormalities are also consistent with myocarditis, although similar changes may be seen in pericarditis or may be the result of nonspecific, acute physiologic or biochemical insult. The elevated transaminases and lactic acid dehydrogenases may to some extent have been contributed to by myocardial inflammation. However, in the light of the greater increase in the SGPT, as well as other abnormal liver function tests, it seems more likely that these reflected hepatic changes.

It should be noted that during the first half of 1962 in the Boston area, the incidence of measles was unusually high, and that reported complications, such as encephalitis and pneumonia, were quite frequent.

Reports of well-documented association of myocarditis and measles are rare in the world literature. Most of the standard reference works fail to mention myocarditis or indeed cardiac involvement at all in cases of measles.

Degen[1] in the clinicopathologic study of 100 fatal cases of measles, found 4 cases of pericarditis, 13 cases of pericardial effusion without evidence of inflammation, some degree of right heart dilatation in 24, and 4 cases in which the myocardium was involved. These latter 4 had a mild degree of cellular infiltration of the myocardium, chiefly lymphocytic, in the perivascular tissue. It was thought that most of these complications were secondary to bacterial suprainfection, particularly with hemolytic streptococci. Neubauer[2] reviewed 200 cases of myocarditis in acute infectious diseases in children. Only 4 cases in this series were measles, and all of these cases ... complicated by severe bronchopneumonia. Saphir[3] in a review of 97 autopsied cases of myocarditis in children found no cases associated with measles. He noted that there were few references in the literature on myocardial changes in measles. Gore and Saphir[4] reporting on an autopsy series of more than 1,400 cases of myocarditis found no cases associated with measles.

There have been some sporadic case reports, most of which have been concerned with conduction defects associated with measles, which presumably were the result of injury to the cardiac conduction system as a result of inflammatory changes. In 1920, Eyster and Middleton[5] reviewed the literature and found 20 cases of A-V block in children, adding 1 case of their own. Most of these represented congenital defects or were the result of diphtheria. One case, that of Hecht, was cited which was questionably due to measles. Lyon[6] described the case of a 30 year old man who presumably developed an arrhythmia during the course of measles; he had persistent sinus tachycardias and right bundle branch block. In 1948, Clark[10] reported on 3 children who had complete heart block which was questionably due to measles. Two of these children were siblings. The relationship to measles was not well documented, and the possibility of rheumatic myocarditis could not be ruled out in 2 of these patients. One of the children died of a Stokes-Adams attack. Perhaps the best documented of the case reports is that of Giustra and Nilsson[5, 11] This was the report of a previously healthy 5 year old child who developed various arrhythmias and conduction defects a few days after having had measles. This patient had bizarre arrhythmias, including tachycardias, as well as conduction defects, and finally died 3 years after the onset of this illness—death occurred during a convulsive seizure which occurred after a tachycardia. At autopsy, generalized subendocardial sclerosis and focal fibrosis of the left bundle branch were found. There was dilatation and hypertrophy of both ventricles, particularly of the right ventricle. No myocardial changes were seen.

There are no pathognomonic electrocardiographic signs of myocarditis. The changes reported have included condu

defects, arrhythmias, and S-T and T wave changes. Fine and associates[1] in a study of 84 cases of myocarditis in acute infectious diseases included 8 cases of measles. In 6 of these 8 cases the electrocardiograms were normal and in 2, borderline. In this same study, artificial fevers were induced in 18 patients; temperatures were maintained at 105 to 106° F. for about 6 hours. In all but one patient there was no clinical sign of cardiac disturbance, and *none had significant electrocardiographic* changes. Bengtsson and Berglund[7] studied the electrocardiograms of 451 patients with measles: 409 were children, and 42 were adults. Changes were seen in 2 children and in 7 adults. These changes consisted of increased P-R interval, elevated S-T segments, depressed S-T segments, inverted T waves, and nodal rhythm (one case). All these changes had resolved within 2 weeks of the onset. There was one case of right bundle branch block which persisted. Ross[8] studied 71 children with measles in an effort to determine whether abnormal cardiac findings in measles were as rare as suggested by the scarcity of case reports. None of the children had known heart disease prior to having measles. None of the patients had signs or symptoms of pericarditis or endocarditis, and there was little clinical evidence of myocarditis. One patient had premature ventricular contractions, whereas the other 70 had regular sinus rhythm, sinus tachycardia, or sinus arrhythmia. Thirty per cent had minimally increased P-R intervals. One child had a right bundle branch block which did not change during the follow-up period; it is not known whether this child had had the bundle branch block prior to measles. In none of the 71 cases were there S-T segment changes. The T waves were normal in the standard leads in all patients; there was some suggestion of an increased incidence of abnormal T waves in the chest leads. Goldfield and associates[12] reported on 395 electrocardiograms taken on 105 patients during the course of measles. Significant changes were considered to include substantially increased P-R intervals and marked lowering or inversion of the T waves in dependable leads (I, aVL, or the left precordial leads), as well as more striking changes. Twenty patients were found to have definite electrocardiographic abnormalities. There was no correlation with age, sex, or the severity of the infection. In commenting upon previous reports of electrocardiographic changes in measles, particularly those relating to heart block, Goldfield states that "when most of the reported cases are carefully considered, no causal connection is firmly established."

The pathologic changes of myocarditis in general, particularly in measles myocarditis, *have not been well defined*.[1,11,14,16] Various pathologic changes have been reported, including cellular infiltration, both interstitial and perivascular in location, muscle fiber fragmentation, fibrosis, and vasculitis. Probably the best pathologic study of the heart in measles is that of Marinesco,[15] who studied the hearts of 28 patients who died while they had measles. Four fifths of these patients died of respiratory complications, the remainder of encephalitis or a concomitant disease. Most of the deaths occurred within 10 days of the onset of the rash. In a few cases, aside from the pulmonary and neurological signs, the patients had signs of cardiovascular involvement which included collapse, cyanosis, weak heart sounds, tachycardia, and embryocardia. In most cases there were some degenerative changes in the myocardium and accompanied in a few by small pericardial effusions. In 3 cases there was hemorrhagic pericardial effusion. Seven of the 28 patients had cardiomegaly. In agreement with other investigators,[14] it was found that cardiac involvement was often associated with pulmonary complications, particularly bronchopneumonia and interstitial pneumonia. Also found were endothelial desquamation and perivascular hemorrhages which penetrated the myocardial interstitium and disturbed the anatomic relationship of the muscle fibers. There were cellular infiltrations with lymphocytes, histiocytes, fibroblasts, and plasma cells. These lesions were seen in 6 of the 28 hearts that were examined.

In a consideration of the pathogenesis of the myocardial changes seen in measles myocarditis, tissue anoxia, vasculitis, circulating myocardial toxins, and direct invasion by the virus have all been incriminated, but this issue is far from settled. In view of the apparent association with

pulmonary involvement it would seem that anoxia might well be the most likely causative factor in a majority of cases with myocardial involvement However the rare case remains such as the present one in which no pulmonary dysfunction is apparent and here myocarditis related to infection with the measles virus is the probable mechanism

Summary

A case of myocarditis which occurred in association with measles in a previously healthy adult has been reported The patient made a full recovery The apparent rarity of this complication is commented upon and the available literature pertaining to previous case reports clinical electrocardiographic and pathological studies has been reviewed and the pathogenesis commented upon

The author wishes to thank Dr M R Davis Chief Medical Service United States Public Health Service Hospital Boston Mass for guidance in the care of the patient and the preparation of this paper and Miss P Bingham for her assistance in the preparation of the manuscript

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T-wave inversion with elevated RS-T segment simulating myocardial injury

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Although many descriptions of the normal S-T segment variant have aided the physicians in distinguishing myocardial injury from S-T elevation due to early ventricular repolarization, little stress has been placed on the frequent association of benign T-wave inversion with early ventricular repolarization.[1-4]

The purpose of this communication is to describe this phenomenon, show its close resemblance to ischemic myocardial injury, and define its distinguishing characteristics. Three cases have been selected for illustration of this point.

Case reports

Case 1. F. W., a 54-year-old Negro man, was seen in the clinic for symptoms of chronic bronchitis. The blood pressure was normal, and careful cardiac examination failed to reveal any abnormalities. The laboratory examination, including electrolytes, was within the normal range. Serial electrocardiograms displayed S-T elevation and T-wave inversion most marked in Leads V_{3-4}, but also present to a lesser degree in Leads V_{5-6} and Leads I, III, and aVF (Fig. 1). Seven electrocardiograms taken over a period of 2½ months showed minor changes in the magnitude of S-T elevation and T-wave inversion without any significant alteration in the basic pattern. At no time were there any subjective or objective evidences of myocardial injury or cardiac dysfunction.

Case 2. D. C., a 26-year-old Negro man, was admitted because of vertigo of 36 hours' duration which developed while he was performing strenuous exercise. The past history was unremarkable. On physical examination he appeared anxious but in no acute distress, and the cardiovascular system was normal. Serial electrocardiograms displayed S-T elevation and T-wave inversion in Leads V_{3-6} (Fig. 2, A). Repeated laboratory determination of serum glutamic oxalacetic transaminase, serum lactic dehydrogenase, complete blood count, erythrocyte sedimentation rate, and electrolytes were normal. The patient was discharged after an uneventful 10 day hospital course.

Case 3. J. H., a 38-year-old Negro man, was admitted for diagnostic studies. The past history revealed mild hypertension of 2 years' duration unassociated with angina pectoris or left ventricular failure. No treatment of hypertension or cardiovascular disease had been instituted. On physical examination a blood pressure of 180/100 mm. Hg, minimal hypertensive changes in the eye grounds, sustained left ventricular impulse, and an atrial gallop were found. The laboratory data were within normal limits. Daily electrocardiograms demonstrated S-T elevation and T-wave inversion in Leads V_{3-6} with slight day-to-day variations in magnitude (Fig. 2, B). The hospital course was unremarkable. The patient was discharged 7 days

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after admission and has remained in good health for the past 8 months

Discussion

The combination of S T elevation and T wave inversion has not received the attention accorded to the benign variety of isolated S T elevation[1, 5] or to the isolated T wave negativity in mid precordial leads[6] Although the most likely explanation is the lower incidence for this combination, the possibility of erroneous diagnosis of myocardial injury in most such cases cannot be excluded Goldman[7] has emphasized that the combination of S T elevation and T wave inversion should not be the sole criterion for the diagnosis of myocardial injury Nevertheless this pattern continues to be accepted as an electrocardiographic support for such diagnosis

Analysis of the tracings in the cases herein reported brings out certain differentiating features (1) S-T segment elevation is most prominent in and often limited to the mid and lateral precordial leads ranging in magnitude from 1 to 3 mm and reciprocal S T depression is absent in leads exploring the negative side of the vector This is not to be interpreted as a point against the dipole theory for as Grant[8] suggests with reference to the

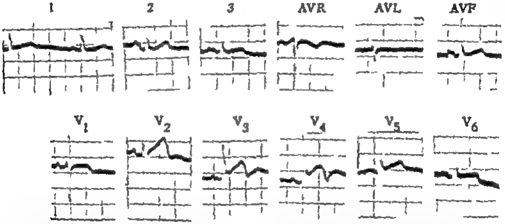

Fig 1 Representative 12 lead ECG in Case 1 showing marked S-T elevation in Leads V the characteristic notch at the end of the R in V and terminally negative T waves Note abrupt changes from rS to R in V Otherwise QRS complexes are normal in direction and amplitude

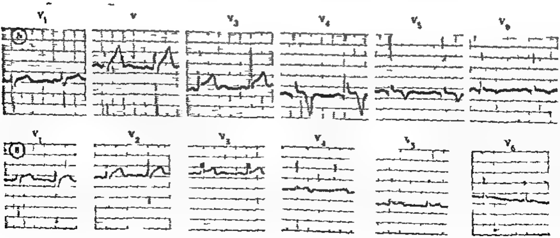

Fig 2 Chest leads in Cases 2(A) and 3(B) showing features identical to those of Case 1 (Fig 1)

isolated T wave negativity; this apparent exception to the vector concept is most likely due to the relatively small magnitude of the vector sufficient only to affect approximate leads; (2) a distinct notch on the downstroke of the R wave immediately preceding and merging with the elevated S-T segment; (3) upward concavity of the S-T segment; (4) a positive-negative biphasic T wave with predominant terminal negativity; and (5) counterclockwise rotation of the QRS vector in the horizontal plane with abrupt loss of S wave simultaneous with the appearance of S-T elevation.

Feature No. 5 has been of some interest to us. It is not confined to the benign variety of S-T elevation; it has been observed in other types of significant S-T elevation, such as that of the hyperacute phase of ischemic myocardial injury. Similarly, loss of the S wave concomitant with the appearance of S-T elevation can be readily seen during pericardiocentesis when the needle converted to an electrode strikes the epicardium and produces a current of injury (Fig. 3). Such needle-electrode assemblies sample predominantly local electromotive forces manifested by rS, RS, or Rs depending on the route chosen for introduction of the needle. When the epicardium is approached, the electrogram shows S-T elevation and "absorption" of the S wave into the QRS, culminating in a monophasic curve with no S wave whatever. The S-T elevation and T wave inversion which occur in the early stage of myocardial infarction are diffuse with reciprocal changes (Fig. 3). The terminal QRS notching is not present and the elevated S-T segment is either plateaued or rises tangentially to merge

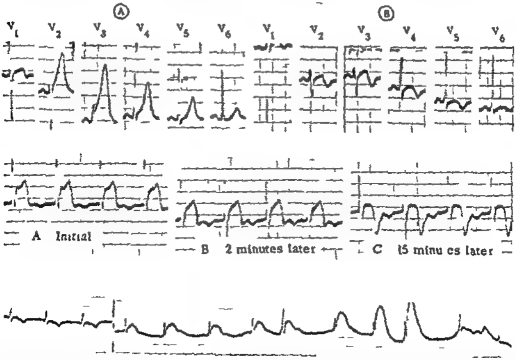

Fig. 3. *Top row A:* Chest lead in a 49-year-old woman taken during the first hours of a developing *acute myocardial infarction, showing characteristic hyperacute ST-T changes and the abrupt QRS* transition in V_4. *Top row B:* Same as in *A* taken 1 day after the onset, showing a more gradual QRS transition and the dome-shaped S-T. *Middle row:* Three segments of a continuous Lead V_4. *A*, initial; *B*, 2 minutes after *A*; *C*, 15 minutes after *B*, in a man in the developing phase of an acute anterior myocardial infarction depicting the hyperacute ST-T changes. Note the gradual return of the S wave as S-T elevation recedes from *A* to *C*. *Bottom row:* Continuous tracings recorded by the needle-electrode assembly during a pericardiocentesis, showing changes of acute injury of contact with the myocardium. Note S-T and QRS changes similar to those of hyperacute myocardial infarction (*top row*).

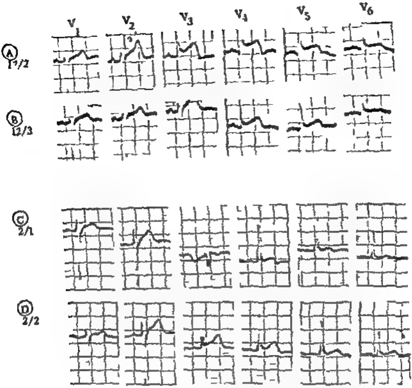

Fig 4 Chest leads taken on two different dates from Cases 1 and 2 showing dynamic nature of terminal T wave negativity Note diminished depth of T wave negativity in B as compared with A and in D as compared with C

with an aftercoming T without displaying an initial upward concavity If an S is present the S T segment starting from the upstroke of the S is invariably dome shaped When the S wave is absent the S T segment originates from the down stroke of the R and merges with the up stroke of the T without inscribing the pattern typical in the benign type In the latter situation which is often found in acutely developing myocardial infarction the T is generally peaked and upright with out terminal negativity The changes of subacute pericarditis bear some resem blance to those of ischemic myocardial injury but are more diffuse in distribution with reciprocal features The T waves remain upright so long as the S T elevation persists

The electrophysiologic explanation of the benign entity discussed here remains obscure most likely it represents an aber ration of the repolarization process akin to that found in the normal S T variant unassociated with T wave inversion[1,2] In fact a transition from one form to another was observed in Patients F W and D C (Fig 4) Wasserburger and as sociates[3] have shown that a majority of patients with early repolarization de veloped precordial T wave inversion with brief hyperventilation In addition it has been estimated that benign S T elevation occurs in approximately 1 per cent of the adult population Since anxiety states chest pain and hyperventilation are inti mately related one can appreciate the magnitude of the problem and the need for a precise differentiation from the patho logic mimics The effects of sedation and exercise upon the ECG pattern were not studied The administration of 40 μg of potassium chloride intravenously to the patient of Case 3 did not change the pat tern Inhalation of amyl nitrite on the other hand brought the S T segment down to a normal level and normalized the terminal T wave negativity However our experience with these procedures is still too limited to allow any conclusio

The racial predilection of the Negro for this ECG pattern is indeed striking All 3 cases of this report as well as other cases of the same phenomenon observed by the authors over the past several years have been in Negroes Although this observation may not be out of keeping with the racial distribution of the patients admitted to our general hospital our experience with the ECG tracings in other institutions with predominantly white populations leads us to believe that the occurrence of this pattern in racial groups other than the Negro must be extremely rare

Conclusion

Three illustrative cases of the benign variety of combined S T elevation and T wave inversion are reported Its resemblance to such processes as ischemic myocardial injury and pericarditis is noted and clues to their differentiation are suggested

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Interventricular septal aneurysm associated with maternal death

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Interventricular septal aneurysms are rare and the condition has been slow to gain recognition Clinically they present a problem of diagnosis which especially if the condition is complicated by rheumatic heart disease may be impossible to solve

Larsen and Noer[4] reviewed the literature and found that only 8 cases including 3 of their own appear to have been reported in the last 25 years Death due to the aneurysm is unusual fatal cases associated with rheumatic involvement are rare death due to aneurysm complicated by rupture of an aortic cusp has apparently not been recorded Similarly maternal death from this cause would appear to be unique Thus the following case report is of interest

Case report

S R a 17 year-old primigravida was first seen in the twenty first week of pregnancy She gave a history of intermittent treatment of rheumatic fever at the age of 11 She had no other illness and had been able to undertake moderate exertion without becoming breathless

First visit Her blood pressure was 120/65 mm Hg There was no edema or albuminuria On auscultation a loud rough systolic murmur was heard mainly over the apical area The possibility of residual mitral stenosis was considered and she was asked to report in 3 weeks time and told that he would probably be admitted for rest

Second visit and admission She gave a history of a fall 7 days earlier since when she had been breathless and had to sleep sitting up Nevertheless she had walked 3 miles to the hospital

On admission she had a tachycardia of 128 per minute her blood pressure was 130/50 mm Hg Her hemoglobin level was 10 2 Gm per cent the liver was three fingerbreadths below the costal margin the heart was enlarged and the apex was $4\frac{1}{2}$ inches from the midline A Grade 3 diastolic murmur was heard over the whole precordium and there was a soft systolic murmur Crepitations were present in both lung bases Digitalis leaf grain 1 twice a day was prescribed

The VDRL report was positive 1 4 the erythrocyte sedimentation rate was 42 mm per hour (corrected) After a week during which she showed occasional cyanosis and the tachycardia persisted a tentative diagnosis of rheumatic carditis was made and prednisone 40 mg per day was ordered

Electrocardiographic readings at intervals showed changes indicative of left ventricular hypertrophy and strain and suggestive of myocardial insufficiency There was no suggestion of bundle branch block The physical signs altered little No clubbing of the fingers was noted By the twenty first hospital day the pulse had become more obviously collapsing and the auscultatory findings gradually assumed the character of aortic incompetence with some stenosis A tachycardia of 130 per minute or more persisted and the dose of prednisone was increased to 60 mg a day Digitalis therapy had been continued except on two occasion when it was stopped for 48 hours because of vomiting Aspirin every 4 hours was given at this stage but the erythrocyte sedimentation rate remained the same X ray examination of the cardiac shadow showed left ventricular hypertrophy

On the thirty fifth hospital day in the thirtieth week of pregnancy the patient had a short fit of twitching Next day a fully developed epileptiform

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Fig 1 Heart opened to how avulsed aortic cusp (with probe in place) and ventricular septal an eurv m immediately below the site of rupture

fit occurred and was followed by a flaccid paralysis for 24 hours Lumbar puncture howed no abnor mality of pressure or content Repeated blood cul ture was sterile

Thereafter becau e the submandibular glands became swollen the do e of prednisone wa reduced Penicillin 4 million units a day was ordered be cause although the diagnosi was quite uncertain the possibility of thrombus formation in the left side of the heart and active rheumatism could not be excluded Her blood urea was 79 mg per cent

By the fortieth day the submandibular swelling had subsided The tachycardia persisted and her blood pressure showed a marked change to a level of 180/30 mm Hg The collapsing pulse was very marked Persistent cyanosis developed and thi wa relieved by the intermittent administration of oxygen

On the forty eighth day in her thirty second week of pregnancy the patient went into spon taneous premature labor Her temperature was 95 F her hemoglobin was 12 6 Gm per cent and her blood urea was 93 mg per cent She was de livered by elective low forceps under pudendal block The patient collapsed and died 5 minutes after de livery with the placenta still in situ

Autopsy findings The significant postmortem findings were es entially related to the cardio-vascular system

The pericardial sac contained approximately 60 ml of serous fluid The heart weighed 344 grams th re was slight bilateral ventricular hypertrophy and the left atrial endocardium showed some thick ening The mitral tricuspid and pulmonary valves were normal and the coronary vessels were not narrowed

The attachment of the left posterior cusp of the aortic valve was found to have ruptured in its middle portion (Fig 1 and 2) On its ventricular surface were calcified vegetation Immediately below thi cusp there was an aneurysm in the membranous portion of the interventricular septum bulging into the right atrium the ostium measured 25 mm in diameter

The placenta was still attached to the posterior wall of the uterus and the cervix was widely patulous and hemorrhagic The parturient uterus weighed 740 grams and was soft and flabby

The postmortem findings in other organs were those as ociated with death caused by acute failure of the left side of the heart

Histology Examination of the ruptured aortic

Fig 2 Same as Fig 1 enlarged showing region of lesions

cusp showed that the vegetations were old and consisted largely of organized and organizing fibrin with a scanty infiltrate of inflammatory cell The thickened aortic cusp was vascularized

Discussion

Deaths due to cardiac causes in pregnant women occur largely in patients over 35 years of age in those with evidence of a history of heart failure and in those with atrial fibrillation[1] Although the younger patient may die of congenital heart disease to die at 17 years of age from a lesion which is not usually considered to be significant is indeed unusual The diagnosis of ventricular septal aneurysm is usually made incidentally as a postmortem finding Edwards[3] states that the finding of such an aneurysm is seldom related to disturbances of clinical significance

In the rare case in which significant changes have occurred the signs and symptoms have been so diverse as to render very difficult the making of the diagnosis The addition of an aortic valve lesion in this case rendered a diagnosis impossible

The origin of the vegetations on the aortic cusp is obscure Although they may have been due to rheumatic fever at the age of 11 the history is not conclusive and one might expect to find some lesion on other cusps It is also possible that the relationship of the cusp to the aneurysm may have resulted in such a growth This is suggested because similar vegetations occur on a single cusp in association with an aneurysm of the sinus of Valsalva[4] Also with a septal defect such endocarditis is known to occur even with a very small opening[6]

The aneurysm was at the site usual for such lesions at the upper part of the septum Histologically the aneurysm was of the usual septal membranous structure above the muscular portion The site of such a septal lesion makes it possible that the attachments of the cusp are less strong than in the normal person A further weakening factor in the present case may have been that the ostium was larger than that usually seen it was fully 10 mm larger than the largest seen by Larsen and Noer[6] This may have allowed more ready dislocation of the cusp

One can postulate that there was degree of aortic incompetence permitted by the site of and the damage to the cusp when the patient was first seen there was a pulse pressure of 55 mm Hg Pregnancy would increase the load on the affected valve and while this load was gradually developing a temporary sudden increase in pressure possibly when she fell resulted in partial rupture of the valve After this the blood pressure altered to 180 30 mm Hg and the pulse became frankly collapsing

It seems probable that complete rupture of the valve occurred during labor and that the subsequent collapse of the patient 5 minutes after delivery was the consequence of aortic regurgitation Such collapse is typical of this condition its mechanism is unknown[1] Convulsive episodes such as occurred 2 weeks before death have been reported in relation to such aneurysms sometimes presenting as in Adams Stokes syndrome[7] Such episodes perhaps point to a greater importance of the aneurysm than the valvular lesion in this patient

Another consistent feature of the clinical history was the persistent tachycardia which was unaffected by digitalization Lesions in the anatomic position of this septal aneurysm may interfere with conduction in the bundle of His Disturbances in rhythm have been found in association with such lesions however Rogers and associates[7] reported sinus tachycardia and idioventricular rhythm for example The persistence of a rapid heartbeat despite lack of symptoms in the early stage of pregnancy in this patient does suggest that the defect may have played some part in the production of the rhythmic change

Alternatively however this may also have been a compensatory mechanism for the regurgitation caused by partial rupture of the valve The reason for the tachycardia must remain obscure

Summary

Interventricular septal aneurysm complicated by affection of the related aortic cusp is discussed

A case is described during the patient s pregnancy the diagnosis was uncertain and she died 5 minutes after premature vaginal delivery

The postmortem findings are recorded. The possible sequence of events which resulted in collapse and death is discussed.

We wish to thank Professor G. Bras of the Department of Pathology and Professor D. B. Stewart of the Department of Obstetrics and Gynecology for permission to publish this case.

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Ionic transfer in cardiac muscle
An explanation of cardiac electrical activity

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The transmembrane potential

To understand the sequence of changes in ionic concentration which explain electrical activity one must first be familiar with records that represent transmembrane action potentials With the perfection of the ultramicroelectrode it became possible to measure the difference in potential between the tip of this electrode located intracellularly and some extracellular point usually nearby during both the resting phase and during excitation of the cardiac fiber These two measurements are called the transmembrane resting potential and action potential respectively Such a record is seen in Fig 1 recorded from a left ventricular fiber of the dog heart During the resting state the interior of the fiber is −90 mv as can be seen at the left of the recording This is followed by activation a swiftly rising deflection which passes through zero and reverses its sign so that at its peak the cell interior is +30 mv It is during this rapid upstroke that the QRS complex of the standard electrocardiogram is written Recovery is defined as the return of this reversed potential difference to the resting level again It takes place in three distinct phases (1) an initial rapid phase (2) a plateau (3) and a final rapid phase[1] It is during the latter that most of the T deflection of the electrocardiogram is recorded

The transmembrane resting potential and the spike of the action potential have been carefully studied and much is known of their genesis The three phases of recovery are of great interest but their origins remain speculative

Basic to an understanding of the problem is the knowledge that at the cellular membrane level electrical current is synonymous with the movement of ions The laws which apply to the literal physical transfer of ions across cardiac membranes are different from the laws which apply to electrical current in the rest of the body These ions may be transported by traveling down a concentration gradient propelled in the other direction by a potential gradient

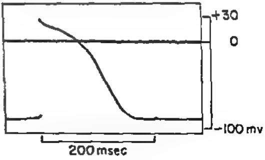

Fig 1 Transmembrane potential from dog ventricle (Reproduced by permission from C McC Brooks et al *Excitability of the Heart* Figure 9B New York 1955 Grune & Stratton Inc)

Presented in part at the University of Minnesota Center for Continuation Study Course in Intermediate Electrocardiography "
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pulled by solvent drag forces or may combine with another membrane constituent and be transferred by external metabolic work. The first method is illustrated by the junction potential produced at the interface of two solutions containing different concentrations of the same ions. If, for example, a concentrated solution of hydrochloric acid touches a dilute solution, both hydrogen and chloride ions tend to diffuse from the concentrated solution into the more dilute solution. The hydrogen ion moves faster and thus the dilute solution soon becomes positively charged because of an excess of positive hydrogen ions. The more concentrated solution is left with an excess of negative chloride ions and thus acquires a negative charge. With the passage of time, the dilute solution accumulates an excess of positive electricity, which retards the velocity of the hydrogen ions and accelerates the velocity of the chloride ions, so that ultimately the two ions move with the same average velocity. As the two solutions acquire the same concentration, no difference in potential will exist between the two solutions, for there are an equal number of positive and negative ions present in each compartment with no tendency for a net improvement in either direction; thus, at equilibrium, electrical neutrality exists.

A useful rule is that the difference in potential produced at the junction of two solutions of different concentration is caused by the rates of migration of the ions present; the more dilute solution acquires a charge corresponding to that of the faster moving ion. This is expressed in the following equation:

$$E = \frac{u - u}{u + u} \frac{RT}{nF} \ln \frac{c_2}{c_1}$$

where c is the activity of the electrolyte in the concentrated solution and c_1 is the activity in the dilute solution, and u and u_a are the migration velocities of the cation and anion, respectively (Table I). R, T, and F are the gas constant, absolute temperature, and Faraday, respectively, and n is the valence. See Table III for values of these constants. Activity may be defined here as effective concentration and is similar to p^H measurements of hydrogen ion concentration. Since the calculations always involve ratios of activity, the actual activity of the ion is of small importance if the activity ratio is proportional to the actual concentration ratio.

Table I. Absolute ionic velocities at 18°C under a potential gradient of 1 volt

H^+ =	3.2×10^{-3} cm./sec.
Cl^- =	69×10^{-3} cm./sec.
K^+ =	66×10^{-3} cm./sec.
Na^+ =	45×10^{-3} cm./sec.

Data from F. H. Getman and F. Daniels: Outlines of Theoretical Chemistry, ed. 6, New York, 1937, John Wiley & Sons, Inc.

The concentration cell

If the two solutions are separated by a semipermeable barrier which effectively blocks one ion, then this particular ion makes no contribution to the difference in potential between the two compartments, and any observed difference in potential must be due to the ions which can penetrate the barrier. The presence of a partial barrier in the form of a membrane or cell wall makes the two solutions act somewhat differently from a junction potential in that certain ions are no longer free to move, whereas others appear to penetrate the membrane with no difficulty. The model presented by the cardiac fiber is that of a membrane separating the intracellular and extracellular spaces with changing permeabilities to each ion species with time. The changes in permeability are least during the resting state and greatest during the rising phase of the action potential.

There are large differences in concentration across this membrane interface and, therefore, a tendency for ions which are freely permeable to move down their respective concentration gradients. But, as in the case of H^+ ion movements in the HCl concentration cell, forces exist to oppose or slow down these movements. This situation is best illustrated by the potassium ion, which is highly concentrated inside the cell and tends to move outward but which is opposed by the attractive force of anions within the cell and repelled by cations, including potassium, outside the cell. Thus K^+ tends

to move outward because of its concentration gradient and inward because of a potential gradient. When these two forces are equal a state of equilibrium exists. Unlike the HCl concentration cell, this equilibrium is not at the point of equal concentration. The relation between the ionic concentration (activity) ratio, temperature, and transmembrane potential for zero flux of the ion specie (equilibrium) is called the Nernst equation:

$$E = -\frac{RT}{nF} \ln \frac{(a)\ \text{inside}}{(a)\ \text{outside}}$$

Since R, T, n, and F are constants at constant temperature of 37 C (310° absolute), and including factors for converting natural logarithms to base 10 and for converting volts to millivolts, this may be more simply stated:

$$E = -61.5 \log_{10} \frac{(a)\ \text{inside}}{(a)\ \text{outside}}$$

When the transmembrane potential equals the equilibrium potential there should be no net flux of this particular ion specie across the membrane. Any change in transmembrane potential away from the equilibrium potential constitutes a driving force to change the ionic concentration gradient in the appropriate direction until a new equilibrium is established. If the membrane potential is greater than the equilibrium potential of the ion, the movement of the ion will be against its concentration gradient, and if the membrane potential is less than the equilibrium potential of the ion, then the ion will move down its concentration gradient. Thus the transmembrane potential which may be the result of movements of both positive and negative ions in either direction will determine at equilibrium the concentration of ions on either side of the membrane.

Transport forces and permeability

The following are the general rules for the net transport of ions across cell membranes. There are only four known kinds of transfer forces involved in the movement of ions. These are (1) differences in concentration, (2) differences in electrical potential between phases in contact with the cell membranes, (3) differences in activity coefficients, and (4) solvent drag force arising from the passage of solvents through the membrane. There are clear instances when the movement of ions can not be explained by one of the above-mentioned processes, and it is customary to reserve the term "active transport" for these instances. In no case has the nature of active transport been clarified, but a specific chemical binding with membrane constituents appears to be essential. It is known that the transport in these instances cannot be explained in terms of the aforementioned physical forces. The transfer of sodium from inside the cell to the outside is thought to be an active transport.

Prior to 1941 it was generally accepted that the muscle membrane is permeable to potassium and essentially impermeable to anions and sodium. It was then that Boyle and Conway introduced a new hypothesis that the muscle membrane is permeable to potassium and cations of the same or smaller diameter in aqueous solutions and also to the smaller anions such as chloride. It was further stated that the critical size for passage of cations is at the potassium level (hydrated ion) or between it and the sodium ion, and that the critical size for the anions is at or near the dimensions of the chloride ion. In short, the critical diameter for free entrance of cations or anions is 8 angstroms (hydrated ion). Thus while K, Rb, and Cs ions can enter the cell at appreciable rates over short periods, Na and Li ions are virtually excluded, and whereas Cl, Br, and NO_3 ions diffuse only slowly, SO_4 ions are practically excluded. Also existing is a mechanism for the slow extrusion of sodium ions which may be continuously functioning, but the net entrance rate of sodium ions in vitro is vanishingly small.[1]

Concentration gradient of cardiac fibers

Cardiac fibers like skeletal muscle are low in sodium and high in potassium content. The actual values determined from dry-cat heart muscle and expressed in milliequivalents per kilogram of fiber or serum water are shown in Table II.[2]

Calcium is present in the serum in low

Table II Resting cell concentrations (mEq /Kg of fiber or serum water)

Intracellular	*Extracellular*
Na^+ 6 5	Na^+ 159
K^+ 151	K^+ 4 8
Cl^- 5 (estimate)	Cl^- 127

From Robertson and Dunihue Water and Electrolyte Distribution in Cardiac Muscle Am J Physiology 177 292 1954

cellularly in bound form There is good evidence to suggest that calcium enters the cell during excitation and may play a role in excitation-contraction coupling[4] but the role it plays in producing either the resting or action potential is small

There are about 158 mEq per kilogram of cations accounted for in fiber water It is fairly obvious that there are an equal number of anions present to establish electrical neutrality within the cell but the nature of these anions is still unknown They are not diffusible through the membrane except for the small quantity of chloride present The following anions have been found chloride phosphates and dicarboxylic amino acids[5] But these total only a few milliequivalents each so that the residual intracellular anions still remain a mystery

An explanation of the resting potential on the basis of a concentration gradient

Hodgkin and Horowicz[6,7] have furnished strong arguments that the resting potential is produced by the potassium and chloride concentration gradients across the cell membrane It is easy to see if this is true why the inside of the cell is negative with respect to the outside for the high concentration of the positive ion, potassium, exists intracellularly and would tend to migrate outward as a positively charged ion whereas chloride, a negatively charged ion is highly concentrated in the extracellular space and would tend to move inward Both movements would tend to make the intracellular space more negative To analyze the problem quantitatively requires certain assumptions The first of these is that the concentration ratio of potassium ($[K^+]$ inside/$[K^+]$ outside) and chloride ($[Cl^-]$ outside/$[Cl^-]$ inside) found is equal to their activity ratios

If the resting potential is to be explained solely on the basis of differences in concentration of potassium and chloride then the second assumption must be made that the membrane is relatively impermeable to other ions but especially to sodium which is present in high concentration extracellularly That these assumptions are approximately correct is shown by the apparent agreement between the calculated differences in potential and the experimentally measured value of −90 mv as shown in Table III At constant temperature the term RT/F becomes a constant so that the resting potential should vary with the log of the potassium or chloride concentration ratio at a time when there is no net ion flux Burgen and Terroux[8] were able to show that this is the case by comparing the measured resting potential while changing the extracellular potassium concentration in cat atrium For extracellular potassium concentrations above 10 mM a plot of resting potential against log potassium concentration gave a straight line relationship

Table III Equilibrium potentials for potassium and chloride concentration cells

$$V_K = -\frac{RT}{F}\ln\frac{(K^+)_i}{(K^+)} = -92 \text{ mv} \quad (\text{inside positive})$$

$$V_{Cl} = -\frac{RT}{F}\ln\frac{(Cl^-)}{(Cl^-)_i} = -86 \text{ mv} \quad (\text{inside positive})$$

R = 8 316 (gas constant) T = 310° (absolute temperature equivalent to 37 C) F = 96 494 (Faraday constant) ( ) refers to concentration in millimoles per liter inside or outside the cell Data taken from Table II

and significantly the action potential was not altered for potassium concentrations between 2 8 to 8 4 mM. Potassium free Ringer's solution abolished all activity as did raising the concentration above 11 2 mM To reduce unwanted intra cellular ionic shifts as much as possible all measurements were made within 10 to 20 minutes This work clearly showed that in the case of heart muscle the movements of potassium could account for the resting potential within a wide range The one difficulty of the unknown intracellular ionic change was overcome in experiments by Hodgkin and Horowicz[7] They noted that the Nernst equation applied to both potassium and chloride and furthermore that if the external potassium and chloride concentration were varied so that the ion product $(K^+)(Cl^-)$ is kept constant there should be no movement of KCl across the membrane in accord with the properties of a Donnan membrane If for example (K^+) is doubled and (Cl^-) is cut in half the ionic equilibrium will not be altered provided that the mem brane potential responds rapidly and rever sibly to this alteration of K and Cl in ac cord with Equation 1 which is simply a re written form of the equation in Table III

$$\frac{(K+)}{(K+)} = \frac{(Cl-)}{(Cl-)} = e^{(VF/RT)} \qquad Eqn\ 1$$

Using a value for $(K^+)_i$ of 140 mM a plot of measured potentials from frog sartorius muscle against calculated values is shown in Fig 2 This shows excellent agreement for potassium concentration above 10 mM This result obtained in frog skeletal muscle is in agreement with Burgen and Terroux work with heart muscle and constitutes good evidence that the membrane resting potential conforms to the model represented by a concentration cell of potassium and chloride ions

The actual amount of current (I) carried by each ion is a product of its conductance and the difference between the transmem brane potential (V) and the equilibrium potential (V for the ion) For the po tassium ion this would be expressed

$$I_K = g_K (V - V_K)$$

Hodgkin and Horowicz[7] have used this relationship to obtain data for potassium and chloride conductance and permeability in frog skeletal muscle by assuming that the membrane is impermeable to other ions and therefore that the two ions carry all of the current during the resting state They further used a value for intra cellular chloride concentration obtained by substituting external concentration and the potential gradient into the Nernst equation These data suggest that when $(V - V_K)$ is positive and potassium ions are moving outward potassium permea bility falls to a low value of 0.05×10^{-6} cm/sec and when $(V - V_K)$ is negative and potassium ions are moving inward potassium permeability rises to 8×10^{-6} cm/sec The same data obtained for chloride suggest that chloride is not greatly influenced by changes in potential or con centration and has a constant permeability coefficient of about 4×10^{-6}cm/sec

This information suggests that for skele tal muscle the relative contribution of

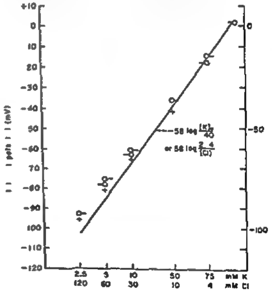

Fig 2 The relationship of resting potential and the log of the transmembrane concentration gradient of K^+ and Cl^- for solutions with $(K_o)(Cl) = 300$ mM[2] Crosses (+) are potentials after equilibrium is established for 10 to 60 minutes circles (O) are potentials measured 20 to 60 seconds after a sudden change in concentration —O after increase in and O— after decrease in (K) (Reproduced by permission of Paul Horowicz Influence of Ions on the Membrane Potential of Muscle Fibers *from* Biophysics of Physiological and Pharmacological Actions Publication No 69 American Association for the Advancement of Science 1961)

K^+ or Cl^- to the membrane potential depends on the direction in which potassium ions are moving, for its permeability is fairly high for inward and fairly low for outward current movements, whereas that of chloride is fairly constant.

The amount of current carried by the chloride ion during the resting phase may be quite different in cardiac muscle than in skeletal muscle. Recent studies by Hutter and Noble[9,10] show that in the resting phase chloride ions account for 68 per cent of the total membrane conductance in skeletal muscle but only a small contribution in cardiac muscle.

The action potential

There is good evidence that the rising phase of the transmembrane action potential is the result of a transient increase in membrane permeability to sodium ions and to the passage of these ions across the cardiac membrane. This information is based on the fact that membrane resistance in Purkinje fibers undergoes a profound decrease[11] during the rising phase of the action potential, which suggests an increase in membrane permeability, and the fact that the action potential of heart muscle, as well as of most other excitable tissues, disappears completely when external sodium is replaced by sucrose or choline. Overton[1] first noted loss of excitability of frog muscle fibers when external sodium concentration was reduced below 10 per cent of that present in Ringer's solution. This observation led to several quantitative studies which showed that the height of the action potential was related to the extracellular sodium concentration.[13,14] Increasing the extracellular sodium above normal levels causes higher voltages of the action potential than are normally found, and a progressive decrease in the extracellular sodium concentration progressively decreases the height of the action potential. When the extracellular sodium concentration falls below 10 per cent of the normal concentration, excitability of the fibers disappears.

A reduction in extracellular sodium causes a small increase in resting potential, but the main change is a decrease in the height of the action potential. In both situations the inside potential becomes more negative, but the effect on the action potential is quantitatively greater. It is significant that varying external potassium concentration, although it greatly affects the resting potential, causes only a slight change in the amplitude of the action potential until the potassium concentration reaches higher levels than those seen in physiologic preparations.

Using the technique of the "voltage clamp" devised by Marmont,[15] Cole,[16] and Hodgkin and associates,[17-19] have obtained direct information that the rising phase of the action potential coincides with the entry of sodium into the squid giant axon. This result was obtained by inserting two electrodes through the length of the cell. One was used to measure intracellular potential, and the other was made to hold the intracellular potential constant or to change it from one value, such as at the resting potential level, to a second value equivalent to depolarizing the cell at constant voltage. The fiber was immersed in a bath divided into compartments, with a pair of electrodes oriented perpendicularly to the fiber and therefore sensitive to movements of current in or out of the fiber. Thus, with a known driving force, the net flux of ions in either direction could be measured. The movements of single ions, such as sodium, could be studied by reducing the concentration of this one ion in the bath and by regulating the clamp voltage so that the sodium equilibrium potential was reproduced, so that the net sodium current would be zero.

For example, when the membrane potential was lowered by 65 mv. from the resting level, there was a transient inward movement of current. This current could be traced to the movement of sodium ions by replacing sodium ion with choline in the external bathing fluid, in which case the inward current did not occur. In both cases there was a delayed, long-lasting, outward current attributed to potassium ions. When the electrical potential was regulated so that it approached the equilibrium potential for sodium, the inward current disappeared, but so long as the polarity of the membrane potential was in the same direction as the resting potential (negative), this inward current was observed. Thus, the net current carried

by the positive charge of the sodium ions is inward unless the membrane potential is made sufficiently large and positive inside to overcome the effect of the difference in concentration The critical value of membrane potential at which the fluxes are equal and the net sodium current zero closely approximated the sodium equilibrium potential calculated by the Nernst equation The delayed and long lasting outward current which is attributed to potassium ion flow is unaffected by changes in the external sodium concentration [19] Changes in external potassium concentration affect it in an unpredictable manner

With the entry of sodium into the cell strong forces exist in the form of both a potential gradient and a concentration gradient to cause the exit of potassium from the cell Wilde and Obrien [1] have clearly shown that there is a pulsatile outflow of potassium with each electrical systole in the turtle ventricle From this point on there is little direct evidence but it is apparent that a mechanism exists for removing sodium from the cell and also that potassium must re-enter to re establish the pre existing ionic gradient There is some evidence that the active sodium transport system in frog skeletal muscle at least is linked to potassium influx This rests on the data of Keynes[** 3] which show that sodium efflux varies fairly promptly and reversibly with extra cellular potassium concentration and that net sodium extrusion from sodium loaded muscle cannot be accomplished in a potassium free media

Summary

The evidence has been reviewed which suggests that the upstroke of the action potential in heart muscle is due to the entry of sodium ions This conclusion is based on the failure of the upstroke to occur if 90 per cent of the sodium is replaced by sucrose and the demonstration of a reduction in amplitude of the rising phase of the action potential with each decrement in extracellular sodium concentration or an increase in amplitude with increasing extracellular sodium concentration In addition the demonstration of a change in membrane resistance of one hundred fold at the time of the rising phase suggests increased permeability of the membrane at this time

The voltage clamp studies in the squid giant axon clearly show an inward movement of current during the rising phase which disappears when choline replaces sodium in the perfusing bath

The resting membrane potential resembles the model of a potassium and chloride concentration cell since calculations based on measured concentrations across the membrane agree fairly closely with measured potentials Furthermore the membrane resting potential is altered in a predictable manner by changed extracellular potassium and chloride concentration but is not appreciably affected by changing sodium concentration Since the skeletal muscle membrane appears to be freely permeable to chloride and only sparingly so to potassium and since potassium permeability is selectively altered during the electrical cycle the chloride ionic concentration gradient is probably dependent on the transmembrane potential and therefore is passive The current carried by the chloride ion in cardiac fibers is small

Little is known of the factors which alter membrane permeability or affect the transfer rates during recovery but it is apparent that sodium is removed from the cell after the rising phase and is replaced by potassium to restore membrane resting potential

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The one-minute abdominal compression test or "the hepatojugular reflux," a useful bedside test

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William A. Pasteur[1] in an 1885 issue of *Lancet* described the effect of filling of the neck veins after abdominal compression as a new physical sign of tricuspid regurgitation. Rondot, before the turn of the century, realized the broader significance of the effect and considered that a positive response indicated weakness of the right ventricle. He named it the hepatojugular reflux. This appeared to be a *meaningful* name because if pressure was applied over a large congestive liver much more jugular distention was produced than with pressure on a normal abdomen. Later authors realized that pressure on the liver was not a necessary part of the procedure and gave it the eponym of the Pasteur-Rondot maneuver.

Hitzig[2] in 1945 was the first in this country to publish observations on the effect of abdominal compression in normal subjects as well as in patients with congestive failure. He applied gradually increasing pressure over the right upper quadrant with the outstretched hand for 1 minute. He concluded, after 16 years of experience with over 2,000 patients, that if pressure on the abdomen has no effect on the cervical veins or if it causes their collapse, it invariably means that the right ventricle is competent while the patient is at rest. If, however, the maneuver causes the cervical veins to become fuller or more palpably tense, it invariably indicates a decompensated right ventricle. The degree of decompensation was considered to be directly proportional to the increased fullness or tenseness.

Hitzig believed that antecubital manometry was superior to visual observation of the jugular veins in judging the effects of abdominal compression. His results in 670 normal patients showed that pressure over the right upper quadrant produced a drop of as much as 2.5 cm. in antecubital venous pressure in 85 per cent of the subjects. He tested the patients under both spinal and general anesthesia because of his belief that the venous pressure might always fall in normal patients who were perfectly relaxed. The venous pressure fell in all 13 of such subjects. When pressure was applied over the left lower rather than the right upper quadrant, the changes were in the same direction but not so marked.

External jugular manometry, however, showed a universal drop in pressure which Hitzig thought was due to the large size of the vessels. This explanation may be inadequate, but the observation is of

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importance when one considers applying the test without manometry.

Transitory rises were sometimes seen in patients without right heart failure; the normal pressure may be followed by a slight rise during abdominal compression with a progressive fall to the control level despite continued compression. These transitory rises do not persist for over 45 seconds. Although Hitzig did not observe an increase in excess of 4 cm., other authors have seen a rise in normal patients as high as 9 cm.[4] These atypical rises were found in patients who held their breath and performed a mild Valsalva maneuver, in patients with increased blood volume, and in patients with incipient right ventricular failure. The only truly false positives in Hitzig's series were produced by occlusion of the superior vena cava below the azygos vein. Drainage of blood from the upper part of the body in these instances must depend on the azygos vein, which, in turn, must have free access to the inferior vena cava. Abdominal compression, by obstructing the flow from the azygos into the inferior vena cava, raises the pressure in the veins of the upper part of the body.

In 1946 Winsor and Burch[5] reported that abdominal compression in normal subjects frequently produced a drop in antecubital venous pressure, even in the presence of ascites, if it were not due to failure. The tendency for venous pressure to fall was less in asymptomatic cardiac patients. Those with congestive failure had the expected rise in pressure, and the greater the degree of failure the greater the rise. These authors used as their zero level the "phlebostatic axis,"[6] which is the mid-sagittal line at the fourth intercostal space. This allowed a common zero level for all body positions. There was a tendency for their patients in failure to have a lower venous pressure in the semirecumbent than in the supine position—probably not a phlebostatic axis artefact because this drop in pressure did not occur in normal patients, and even the effect of abdominal compression tended to be less in patients with failure in the semirecumbent position.

Correlation with the clinical picture suggested that progressive failure with increasing edema was more likely to produce an abnormal rise in venous pressure in response to abdominal compression than was compensating failure with decreasing edema.

Hultgren[7] found that 1 minute of abdominal compression raised antecubital venous pressure higher than did exercise or leg raising. The effect of an incidental Valsalva maneuver was obviated by instructing patients to breathe quietly with the mouth open, and by applying increasing pressure until the patient indicated his level of discomfort. Results were the same with pressure over the epigastrium or right upper quadrant, but were less marked when pressure was exerted over the left lower quadrant. His patients with purely left-sided failure usually had the same responses as did normal individuals. One patient in the sixth month of pregnancy with congestive failure had a pronounced fall in venous pressure. He postulated that abdominal compression trapped blood in the placenta, thereby decreasing the circulating blood volume. He confirmed good correlation between the degree of response to compression and the degree of failure. There was no difference between peripheral and central venous responses when compared via a cardiac catheter during leg raising, exercise, or abdominal compression.

Beem and Thomasson[8] found that in normal patients, although compression of the abdomen produced the usual fall, no change, or a transient rise in the right atrial pressures, it also produced large increases in the pressures in the inferior vena cava and the iliac veins.

Matthews[4] applied a 24 pound weight to the abdomen and noted the effects on simultaneously recorded intrathoracic and superior vena caval pressures, thereby deriving an actual venous or filling pressure (right atrial minus intrathoracic pressure). In normal subjects the central venous pressure responded to abdominal compression either by a fall or by a transient rise. The extent and duration of the rise was greater in patients with heart failure than in normal subjects. A normal response was often noted after diuresis in patients who had been in congestive failure. He concluded that a large sustained rise in venous pressure on compression of the abdomen indicated congestive failure. One patient

with failure responded with such a marked fall in intrathoracic pressure that the rise in filling pressure was counterbalanced thus producing a false negative venous pressure response in a patient who actually had a rise in filling pressure No explanation can be given for this marked drop in intrathoracic pressure on inspiration because the instructions to his patients concerning breathing were not published Another patient responded with such a marked rise in intrathoracic pressure that he produced a false rise in the venous pressure Although Matthews explains that the response to abdominal compression in emphysematous patients may raise their intrathoracic pressures higher than in the normal subject he does not state whether this patient with a marked rise in intrathoracic pressure had emphysema These false changes in venous pressure led him to conclude however that abdominal compression was not a useful test for heart failure

In 1959 Hitzig[9] confirmed Matthews's findings that a rise in venous pressure on abdominal compression was a common finding in chronic lung disease with emphysema or asthma He also confirmed Hultgren's findings that the response of the venous pressure in patients with isolated left heart failure was the same as that in normal subjects

In the same year Moia[10] author of three cardiology textbooks and over 150 publications wrote that manometry may be of great value through the use of certain procedures which provoke a *rapid rise in* venous pressure such as pressing the abdomen raising the lower limbs and giving intravenous infusions Moia thought that compression of the abdomen was the simplest method and preferred the use of the lower quadrants since the upper quadrants were sometimes tender as a result of liver congestion He notes that in patients without cardiac failure forceful compression over the abdomen during normal breathing does not raise the venous pressure by over 2 cm of water This limit however is exceeded in patients with right heart failure and also the external jugular veins become engorged as the height of the column of blood within them rises He also observed that the amplitude of pulsations often decreases even in tricuspid regurgitation

Mechanism of the effect of abdominal compression in normal patients

Hitzig[9] explained the effect on normal patients as being due to a tourniquet effect on the distal inferior vena cava The reduced return from below decreased the resistance to blood from the superior vena cava and its tributaries thus dropping the pressure in these vessels The relation between the right ventricular output and the decreased venous pressure was not clear Hussey and Jeghers[11] accepted this same mechanism as the explanation for the phenomenon

In support of the concept of tourniquet effect, Hitzig[9] and others[5,11] noted that with abdominal compression the femoral venous pressure rose as high as 350 mm of water the rise was proportional to the degree of abdominal pressure The Bradleys[1] also observed a rise in femoral venous pressure when tourniquets were applied to the abdomen Ebert and Stead[13] had shown that about 500 ml of blood sequestered in the lower extremities by venous tourniquets could lower proximal venous pressures Warren and Stead's finding that the jugular veins showed a greater drop in pressure than did the antecubital veins is of importance to the nonmanometric use of the test[14]

Matthews[4] showed that the transmission of a fall in intrathoracic pressure to the superior vena cava was an additional cause of the fall in venous pressure observed in normal individuals When a weight is applied to the abdomen of a normal person who does not resist the upward force against the diaphragm by trying to push away this weight the thoracic musculature takes *over most* of the diaphragmatic work This is accomplished by expanding the chest and breathing in a more inspiratory position which in turn lowers intrathoracic pressure This explains why the severely emphysematous patient who must use the diaphragm to ventilate will resist the weight thereby raising both intra abdominal and intrathoracic pressures The venous pressure which reflects the high intrathoracic pressure will then rise even in the absence of heart failure

Mechanism of the effect of abdominal compression in heart failure

Hitzig[4] postulated that the failing right ventricle raised venous pressure by acting as a mechanical obstruction to the extra blood that abdominal compression forced into the heart. Hultgren[7] included this "backing up of blood" explanation in his theory but added the possible contributing factor of increased venous tone.

Aware of the weaknesses in the "backward failure" theory of the cause of the increased venous pressure in heart failure, Burch[1] in 1951 proposed and then set out to prove that not only the high venous pressure but also the rise due to abdominal compression in patients with failure was due in part to increased venous tone. By "venous tone" he meant the tightness or squeeze which the walls of the veins exert on their contained blood.

Venous tone or distensibility has been studied extensively by plethysmographic methods. This makes use of some derivative of Laplace's law that the pressure in a distensible tube varies directly with the tension in the wall and inversely with its radius. The plethysmograph, because it can measure changes in volume which can be correlated with concomitant changes in pressure, makes possible the derivation of tension.

A digital plethysmograph was used by Burch[18] when he found, in 1954, an increase in venous tone in the digital vessels of patients who were in heart failure. Forearm plethysmography by both Wood and his associates[17] and Sharpey Schafer[13] showed decreased forearm distensibility or increased venous tone in every patient with congestive heart failure. When the failure improved, the venous tone diminished.

Sympathetic blockade has been used by many workers to test for increased venous tone in failure and also to decrease this tone as a mode of treatment.[11, 6] Not only did the venous pressure in the antecubital veins and the tone in the digital veins decrease, but clinical improvement appeared to vary as a function of the decline in venous pressure. Freis and associates[1] gave ganglionic blocking agents to hypertensive patients and found that the blockade could cause an increased cardiac output and a significant fall in peripheral resistance only if the patients were in heart failure. He concluded, therefore, that hypertensive patients in failure have a vasoconstrictive mechanism different from that which normally causes hypertension. Ellestad and Olson[22] demonstrated that remarkably small doses of intravenous ganglionic blocking agents were followed by dramatic improvement in acute pulmonary edema in both normotensive and hypertensive patients.

Burch[23] was able to demonstrate the mediator of the increased venous tone in failure by isolating a length of forearm vein between clamps and finding that, even though it were cut off from the general circulation, the pressure on the isolated segment was higher in patients who were in failure than in subjects who were normal. He did not believe that collateral vessels which supplied the venous segment could have played a part, because the pressure in the isolated segment was always higher than in the adjoining veins. This suggested, therefore, a neurogenic mechanism for the increased tone. He tested this thesis further by injecting a ganglionic blocking agent into the contralateral arm. The pressure in the isolated venous segment fell, and he had further evidence that the increased venous tone was mediated by a reflex. He also found that abdominal compression alone could reflexly raise pressure in an isolated venous segment and that the infiltration of procaine into the segment could abolish reflex rises in pressure.

Having established the reflex increase in venous tone in heart failure, Burch offered the following explanation for the effect of abdominal compression. Veins are set normally at a proper tone to maintain a normal venous pressure, as shown by the fact that they can relax their walls considerably to accommodate a change in volume of many hundreds of cubic centimeters without an appreciable change in pressure.[1] Patients in congestive failure, however, have their venous system adjusted for high tone in order to maintain a tight squeeze around the enclosed blood. Therefore, when pressure over the abdomen displaces blood from the splanchnic area, the displaced volume is forced into

poorly distensible vessels thus raising the venous pressure That a change in blood volume may play a part was strongly supported by Burch s observation[5] that a phlebotomy of 800 c c in congestive failure produced the same effect as ganglionic blockade in that both the venous pressure and the abdominal compression test return to normal That venous tone plays a part was further supported by the observation that with ganglionic blockade the venous pressure of patients in congestive failure was seen to fall before any measurable effect on arterial pressure was noted

Role of the right ventricle in the abnormal compression test response

There are still those who believe with Rondot and Hitzig that during abdominal compression it is the right ventricular failure alone by causing the displaced venous blood to back up mechanically behind it that causes the further rise in venous pressure In order to support this thesis it is necessary to believe that right ventricular failure can elevate venous pressure *without the help of increased venous tone* This is the basis of the so-called backward failure theory

When Starr[26] found that destruction of the right ventricle in anesthetized dogs produced no elevation in venous pressure the backward failure theory began to be questioned seriously It has been pointed out that many patients have low cardiac outputs at rest but normal venous pressures especially patients in failure after the use of diuretics and patients with myxedema It is also known that normal or high cardiac outputs may be associated with high venous pressures after heavy exercise severe anemia and in cases of beriberi

Further experiments supported these criticisms of the backward failure theory Stead and Warren[27] produced sudden variations in right ventricular output by many devices such as temporary occlusion of an A V fistula light exercise and reactive hyperemia of the lower extremities with thigh tourniquets but could demonstrate no significant change in central venous pressure Guyton[28] found in anesthetized dogs that severe obstruction to both venae cavae could produce a rise in venous pressure of no more than 60 mm of water and concluded that considering the venous resistance of these studies comparable to cardiac resistance in heart failure even infinite resistance acutely applied would be incapable of elevating peripheral venous pressure to the high values often observed in heart failure Bakos[9] repeated Starr s extensive damage to the right ventricle of dogs and the venous pressure rose to only 10 to 20 mm of water despite the absence of all contractions of the free wall Even when the left ventricle was also damaged and the pulmonary and systemic pressures began to drop a few minutes before death there was no evidence of increased venous pressure in these anesthetized dogs

Stead[19] and later Burch[19, 0] based their lack of support for the backward failure theory on hydraulic reasoning The argument is essentially that the stroke volume of the left ventricle can never for very long be more than the stroke volume of the right ventricle (after the insignificant 500 c c of lung blood has been ejected) Therefore there is no significant amount of blood available for backing up

How then does the right ventricle contribute to the increased venous pressure seen in heart failure? If the right ventricle were to respond to an increased venous pressure by following Starling s law for more than a few beats its output ought to increase for as long as the venous pressure was elevated and patients with left ventricular failure would be put into acute pulmonary edema The right ventricle succeeds somehow despite a high filling pressure in keeping its output down to levels that can be managed by a failing left ventricle Far from failing in the sense of being incapable of a higher output the right ventricle can respond to a low left ventricular output by some compensatory mechanism that may be connected with the dependence of right ventricular contraction on the anatomically intertwined left ventricle[31] This implies that in congestive failure the right ventricle either is insensitive to changes in venous pressure or is on the downslope of the Starling curve so that an increase in filling pressure causes no change or even a fa cardiac output

That right ventricular failure is not at *all necessary for an increased venous pressure and positive abdominal compression test is easily demonstrated by injecting* sympathomimetic drugs into normal patients and noting a rise in peripheral and central venous pressure that cannot be decompressed by the small increase in right ventricular output that it may produce.[11,27] We have injected metaraminol into 4 healthy subjects and noted not only a rise in antecubital venous pressure to the level seen in heart failure but also a markedly positive abdominal compression test.

The part played by the right ventricle in the production of an elevated venous pressure may now be explained. The low output relative to tissue need is in some way responsible for a sympathetic discharge that increases venous tone which in turn sends blood to the right ventricle at a higher pressure. The right ventricle however does not respond by an adequate increase in output and may even respond with a decrease in output if the patient has a low left ventricular output. This obstructs venous return and allows the venous pressure to rise. Therefore although the elevation in venous pressure is *initiated* by increased venous tone it is *maintained* by the peculiar lack of right ventricular response to increased filling pressure. Thus the backward failure theory may be used to explain elevated venous pressure only if one includes the presence of increased venous tone.

We may now explain satisfactorily the effect of abdominal compression on patients in heart failure. As Burch[19] pointed out the increased tone associated with failure causes the blood that is displaced from the splanchnic area to move into a venous system that is tight. This raises venous pressure throughout the entire venous system. The right ventricle then contributes to the effect by not responding to the increased filling pressures caused by the displaced blood even if the pressure is kept elevated for 1 minute.

Clinical uses of the abdominal compression test

1 As an aid to manometric venous pressure methods. It is often difficult to be certain whether borderline values are *normal or abnormal because depending* upon technique the normal values for *antecubital venous pressure have a wide* range. But no matter what the absolute level of venous pressure may be if abdominal compression does not raise the column over 2 cm venous pressure may be presumed to be normal. If on the other hand it remains elevated over 2 cm for 1 minute of abdominal compression the venous pressure is elevated regardless of a seemingly normal precompression value.

2 As a rapid test without manometry for increased venous tone due to any cause such as heart failure or hypervolemia. The test may be performed both in the supine position or at a 45-degree chest angle.[23] In the supine position changes in distention of the jugular veins are most readily visible. Hitzig[4] has already described the positive and negative results in this position. At 45 degrees however one has the advantage not only of learning the absolute level of venous pressure by measuring the height of the top level of jugular pulsations above the sternal angle of Louis but the positive test will show a persistent vertical elevation in the top level of over 1 cm. Thus the jugular veins may be used as a manometer so that elevations can be quantitated.

3 As a test for the site of superior vena caval obstruction.

The foregoing review of the literature suggests that the following precautions be used in order to obtain reliable results. (1) Help the patient avoid involuntary resistance by gradually increasing the pressure and asking him to inform you of any discomfort. (2) Apply maximum pressure with minimum discomfort by either opening the hand widely or using two hands. (3) Prevent minor Valsalva maneuvers or hyperventilation by asking the patient to breath with the mouth open. (Hyperventilation may cause increased venous tone.[26]) (4) Note the effect on the jugular veins only during inspiration to avoid the false rises that may be produced during expiration by bronchospasm or other causes of minor Valsalva maneuvers. (5) Maintain compression for at least 1 minute to distinguish transient from persistent elevations. (6) Press on the right

upper quadrant but if tender use other areas even at the cost of less pronounced results

We agree with Fowler[34] that the test should be performed not only with the patient supine but also at the 45 degree chest angle and we have used this method on over 500 patients We have found that all patients with elevated venous pressures had a rise in jugular venous pressure of at least 1 cm on abdominal compression that many with normal venous pressures but with signs of congestive failure had an abnormal rise and that almost all patients with acute infarctions of the myocardium had an abnormal response to abdominal compression On several occasions we have supported a diagnosis of an acute infarction because of a positive compression test when other criteria were inconclusive later to have the infarction confirmed by enzyme and electrocardiographic changes

Our technique has been to first test the effect of abdominal compression on jugular distention with the patient in the supine position Then the patient is propped to a 45-degree angle and by a modification of Leishman s technique[37] the absolute venous pressure is measured by placing one end of a spirit level at the top level of the venous pulsation The other end is placed against a ruler that rests vertically on the sternal angle The top limits of normal for this method are known to be about 4 cm Then by means of the abdominal compression test one can in 1 minute tell whether the venous pressure is in the normal range If the exact quantity of abdominal compression needs to be standardized for accurate assessment of the effects of various procedures or treatments one may use the hepatojugularometer designed by Burch[33]

Summary

A history of the abdominal compression test has been presented from the point of view of first showing the techniques used and the remarkably constant results obtained since its introduction 78 years ago and then showing the evolution of theories concerning the mechanisms of both the normal and abnormal responses of venous pressure The backward failure theory is discussed to show its inadequacy as an explanation of elevated venous pressure in heart failure in order to synthesize a new theory based on both the old backward failure and the new concept of increased venous tone The abnormal abdominal compression test mechanism in the light of this approach is therefore readily explained The advantages of applying the test in both the supine and 45 degree chest angle positions are discussed and the various uses and pitfalls are described so that it may be more widely and intelligently used as a routine part of every physical examination

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Electrical conversion of arrhythmias

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Within the last 2 years great attention has been focused upon the use of direct current (DC) shock externally applied for the conversion of a variety of acute and chronic arrhythmias.

The observation that suitable electrical current could arrest ventricular fibrillation in an exposed dog heart is an old one, having been reported in 1899 with both alternating current and capacitor discharge or direct current.

In human beings, Zoll and his associates established that successful defibrillation of the ventricles could be achieved with alternating current (AC) applied through a closed chest. These observations have been confirmed by many other groups. More recently, closed chest AC countershock has been successfully employed in human beings with arrhythmias other than ventricular fibrillation, that is, ventricular tachycardia, supraventricular tachycardia, atrial flutter and fibrillation. Lown and his associates have recently advocated the use of DC shock as a replacement for AC countershock in the treatment of ventricular fibrillation, ventricular tachycardia, and supraventricular arrhythmias on the basis of greater safety and efficacy.

It has been demonstrated that the short duration of the direct current shock (1.25 to 2.5 milliseconds as compared to 150 milliseconds for a standard AC defibrillator) combined with electronic triggering so that the shock is initiated 20 milliseconds after the R wave of the electrocardiogram, avoids the vulnerable phase of the cardiac cycle, which occurs about 30 milliseconds preceding the apex of the T wave. This lessens the chance of ventricular fibrillation which may occur with random application of the impulses. From a study of 10 dogs with repeated AC shocks and 15 with repeated DC shocks over an interval of 45 minutes at the minimal countershock level necessary to revert 65 per cent of the episodes of ventricular fibrillation, it has been noted that AC as compared to DC countershock produced a higher incidence of episodes of ventricular fibrillation (17 vs. 1.9 per cent), atrial fibrillation (66 per cent vs. 0), myocardial infarction (9 of 10 vs. 5 of 15 dogs), and death (5 of 10 vs. 0 dogs). Ventricular premature beats occurred with equal frequency in the two groups, and complicating ventricular tachycardia was slightly more frequent with DC shock (29 vs. 17 per cent). Moreover, of 10 dogs with ventricular fibrillation, AC was effective in defibrillation in 9, but in 1 animal numerous AC shocks up to 750 volts were ineffective in defibrillation, although this animal was defibrillated with one DC discharge. Further evidence for the enhanced efficacy of DC countershock in defibrillation as compared to AC countershock has been demonstrated in hypothermic dogs. At esophageal temperatures from 30 to 20° C. induced ventricular fibrillation was successfully reverted with DC shock in 98 per cent of the episodes, whereas AC

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countershock was successful in reversion of the arrhythmias in 72 per cent. DC countershock was successful in each instance in which AC countershock did not succeed.

Although some difference of opinion has been expressed by investigators concerning the relative efficacy of DC and AC countershock—some find DC countershock effective in defibrillation and others find it less effective than AC countershock—possible support for the greater safety of DC countershock appears to be afforded by pathologic studies. Somewhat less histologic myocardial damage has been found after DC than after AC shock, although precise comparison of dosage in the two methods is difficult.

The clinical use of DC countershock has advanced rapidly since its initial introduction. Because of objections to AC countershock based on the previously mentioned experimental data, and the occasional finding of ventricular fibrillation with the use of transthoracic AC countershock in human beings, Lown and his associates have utilized programmed DC countershock in the treatment of a variety of acute and chronic supraventricular arrhythmias and in ventricular tachycardia in closed chest human subjects. The impulse is delivered 20 milliseconds after the R wave peak. Their most recently reported experience is with over 100 patients, mainly with supraventricular arrhythmias, particularly atrial fibrillation. Successful conversion to normal sinus rhythm has been accomplished generally with one or two shocks in over 90 per cent, with no reported complications from the procedure or from the light general anesthesia required for its use. Other published experience with this technique has in general confirmed Lown's observations. There are undoubtedly many more instances of the successful use of DC countershock in various centers throughout the country which have not as yet been published, and the indications are that Lown's impressive results are being confirmed by other investigators. With its use in atrial fibrillation due to rheumatic heart disease, prior anticoagulation has been recommended when feasible, as well as the prior administration of quinidine. Theoretical objection might be raised to the use of a "suppressive" drug prior to countershock in that it might prevent a focus from assuming a role as pacemaker after countershock, but such an occurrence has not been established clinically.

Although it may not be valid to extrapolate the experimental demonstration of greater safety of repeated DC shocks in the dog to a clinical situation in human beings, it is apparent that DC countershock as presently utilized is generally safe and effective. Even with properly timed DC countershock, however, ventricular fibrillation has been reported. In the case reported, it was easily reverted with a second shock. A comparison of the efficacy of the two methods in human beings is probably not possible with any degree of accuracy at this time because very few instances of the use of AC countershock for arrhythmias other than ventricular fibrillation have been reported in human subjects. However, the case of one patient has been reported in whom it has been shown that external AC countershock (up to 750 volts) was ineffective in defibrillating the ventricles, whereas external DC countershock (160 watt seconds) succeeded. It is likely that sufficient experience may never be acquired to compare the efficacy and safety of AC and DC countershock in human beings with arrhythmias other than ventricular fibrillation in a statistically valid manner, since the bulk of future observations with these arrhythmias will probably be with DC countershock.

It is already apparent, however, that transthoracic electrical conversion of arrhythmias represents a useful clinical modality in various situations: in the conversion of arrhythmias which do not respond to appropriate drug therapy or in which hazardous amounts of drugs must be used for conversion, in situations in which undue delay may be encountered in administering the drug, when precise electrocardiographic interpretation of the arrhythmia is not feasible so that it may be difficult to decide on appropriate drug therapy. In chronic atrial arrhythmias such as atrial fibrillation due to rheumatic heart disease, there is no evidence as yet, nor is there reason to believe, that electrical

conversion to sinus rhythm will be any more permanent than drug conversion provided that similar maintenance schedules of quinidine or procaine amide are used. In acute arrhythmias which seriously compromise cardiac output, countershock may result in prompt, dramatic and permanent return to normal sinus rhythm with rapid improvement in the patient's clinical state. Although general anesthesia is required in most instances, under certain circumstances, particularly when conversion can be accomplished with 100 watt seconds or less, the procedure can be performed without anesthesia. There is some indication that an anterior posterior placement of the electrodes may diminish the voltage required for defibrillation and permit more procedures to be performed without anesthesia. In many instances it is conceivable that the greater simplicity of countershock and the need for relatively less precise electrocardiographic interpretation of complicated arrhythmias may cause this method to be used without any attempt at drug therapy despite the necessity for general anesthesia. There is some tendency in certain centers to adopt this view at present but the general acceptance and application of the method has not yet reached this stage at the present time.

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Recording high-frequency components with a conventional direct-writing electrocardiograph and a four-speed FM magnetic tape recorder

Multiple speed magnetic tape recorders have been used by engineers for some time to alter the time scale and frequency characteristics of recording. Most direct-writing electrocardiographs have a limited frequency response. A multiple speed magnetic tape system can easily extend the range of frequencies that can be recorded by the direct writer so that it can display high-frequency components which previously were obscured. These high frequencies are found much more often in subjects with coronary disease than in normal control subjects.[1-4]

High frequencies can be revealed by the following method using a direct writer. The signal from an electrocardiographic lead is recorded through a high-gain preamplifier on an FM magnetic tape recorder. The tape speed for recording is 30 inches per second. This tape is then played back at a speed of $3\frac{3}{4}$ inches per second, which gives an eightfold expansion of the time base and an eightfold multiplication of the frequencies that can be recorded. The direct writer is run at a paper speed of 50 millimeters per second; therefore the time expansion in the final record results in a time scale of 400 millimeters per second. In a similar manner, the virtual frequency response of the Viso 100 used in this experiment is extended from the standard frequency response of 120 cycles per second to over 500 cycles per second, the range which we found to be necessary for high-frequency electrocardiography.[2] Another requirement is an amplification for the entire system (preamplifier, tape recorder, and Viso 100) that will give large deflections on the direct writer, usually 30 to 40 millimeters per millivolt. The combination of frequency multiplication, time scale expansion, and amplification just mentioned proved to be optimal for the Viso 100. Therefore any change in these factors could result in an inadequate display of high-frequency events.

Electrocardiographic leads from patients who had recovered from myocardial infarctions were recorded on magnetic tape and then played back on the Viso 100. First, leads were made in a conventional manner except that a special paper speed of 100 millimeters per second was used to give better resolution. In these records no high-frequency notching or slurring was seen. However, on records taken from the same strips of magnetic tape an abnormal number of high-frequency notches and slurs were visualized on the Viso 100 when the above-described method of time expansion and frequency multiplication was employed. Such records compared favorably with those made using a cathode-ray oscillograph which had a high-frequency response and photographically recorded with a high-speed camera.

Although the magnetic tape recorder we used, the Ampex FR 1100, is relatively expensive, there are much less expensive four-channel FM tape recorders in production. This combination of a multiple-speed FM magnetic tape recorder and the Viso 100 provides a quick and relatively simple method for recording either high-frequency components in the electrocardiogram or, if desired, the first derivative of the electrocardiogram,[5,6] which has been named the "velocity electrocardiogram" by some investigators.

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Subendocardial hemorrhage in hypotension treated with norepinephrine

Recent work has stressed the futility of treating hemorrhagic shock with pressor agents. Indeed Kory, Close, and Lubitz[1] have demonstrated that norepinephrine is actually contraindicated. The mortality in a well-controlled study of dogs in hemorrhagic shock increased from 33 to 60 per cent when norepinephrine was given in the attempt to sustain arterial pressure. Hackel and Catchpole[2] came to the same conclusion in a similar study one year later. In both experiments the careful control gave an opportunity to reach firm conclusions that is not possible in clinical work.

What is not generally recognized is that special dangers accompany the prolonged use of pressor therapy in hypovolemia. They have nothing to do with the failure of the pressor agent to get at the root of the problem and increase the diminished circulating blood volume. Rather these reasons are concerned with the damage that the heart may inflict on itself under these circumstances.

As was pointed out in a recent symposium on Catecholamines in Cardiovascular Pathology, the incidence of subendocardial hemorrhage associated with pressor therapy of hypotensive states has become a matter for concern.[3] These lesions, at first confined to the immediate subendocardial layer in the left ventricle and characteristically disposed along the papillary muscles, may in severe cases extend deep into the myocardium.[4] Their influence upon the conductive tissue is suspected[4] and, although they are probably inconsequential if mild, they may well impose a burden on an already heavily taxed organ if they are severe.

Recent work by Martin, Hackel, and Sieker[5] has confirmed our earlier studies[7] explaining the mechanism by which the heart damages itself when beating violently in states of diminished blood volume. They employed the same technique utilizing two catheters, one tipped with a pressure sensitive pickup. The latter was placed in the ventricle, the other in the aortic arch. In normal circumstances the pressure curves will be congruent up to the point of closure of the aortic valves, but if epinephrine is given to an animal in shock the low aortic pressure is exceeded by the systolic pressures recorded in the ventricle. The clue to this paradox is the poor filling of the left ventricle. Its powerful muscle, stimulated by the catechol, rapidly completes the ejection phase and, leaving no residual volume, continues to squeeze upon the now empty chamber. The pressure as recorded by a catheter trapped among the trabeculae rises far above that in the aorta beyond. The shearing and squeezing forces so developed are most marked in the regions provided with the least counterpressure. Capillaries rupture immediately under the endocardium and ecchymoses develop whose extension depends on the severity and duration of the condition.

There is adequate supporting evidence to show that this is indeed the mechanism by which the heart damages itself. Kory, Close, and Lubitz[1] demonstrated subendocardial hemorrhage in 2? of 23 hypotensive dogs treated with norepinephrine. Only 2 of 20 controls showed any such hemorrhage if the catechol was omitted.[1] The authors in their original studies observed that normal animals even if killed with adrenaline did not develop subendocardial hemorrhage. Despite their powerful heartbeats the delicate subendocardial tissues were completely protected by the pressure-equalizing effects of the residual volume in the ventricle.[8] The literature is replete with observations which support this theme. One of the most impressive is that describing the universal appearance of subendocardial hemorrhage in exsanguinated, struggling kosher slain cattle and its absence from those slaughtered by stunning.[9] The rarity of these hemorrhages in the subendocardium of the weaker right ventricle is to be expected on the basis of a mechanical origin stemming from the self-destructive effects of the heart's own powerful contractions.[8] The development of catecholamine-induced hemorrhages in hypotensive patients with normal blood volume[10] in whom there is poor heart filling is also possible.

Hence all indications point toward a restrained use of this powerful pressor agent. This has been repeatedly urged by Szakacs.[3] It is his contention that dosage should not be based on the response of the blood pressure, for this will often fail to attain desired levels, but that it should be restricted to the known safe limits as established by studies in animals. It is the purpose of this annotation to point to the mechanical reasons why norepinephrine should be used with great caution under all circumstances in which effective blood volume may be decreased and heart filling poor.

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Renal cortical calcification after snake bite

Bilateral renal cortical necrosis is uncommon and survival rare The clinical syndrome consists of the abrupt onset of oliguria which proceeds to anuria and uremia with lumbar pain and possibly hematuria blood pressure is normal or slightly elevated The condition is due to bilateral symmetrical patchy or diffuse cortical necrosis with sparing of the medulla and a thin subcapsular cortical rim Possible associated lesions include necrosis of the anterior pituitary and adrenal glands [1] Lauler and Schreiner[2] attribute the first description to Juhel Renoy [3]

The incidence of cortical necrosis is difficult to establish since only renal biopsy gives a definite diagnosis during life but less than 200 examples have been reported The numerous causes[2,4,5] fall into three main groups (a) in women it is usually associated with accidental hemorrhage or toxemia in the last trimester of pregnancy (this group forms more than half of the total) (b) in men overwhelming infection causes bacterial shock (c) in children vomiting and diarrhea produce dehydration

Other causes include incompatible blood transfusions[6] multiple fractures and internal hemorrhages severe burns[7] peritonitis streptococcal infection and phosphorus poisoning [8] Subsequent renal cortical calcification has been reported only five times [9] Lloyd Thomas and associates[10] described a radiologic tram line cortical pattern

Our patient developed severe bilateral renal cortical necrosis after snake bite Partial recovery occurred after hemodialysis but subsequently extensive bilateral renal calcification developed This appears to be the only reported case of calcified renal cortical necrosis after snake bite

A 50 year-old married woman sustained a snake bite (probably from a saw scaled sand viper) on the right ankle in Kenya on Sept 9 1961 Incision was made and local treatment applied Next day hematemesis occurred and anuria developed During the following week a hemorrhagic state developed with ecchymoses epistaxis further hematemesis melena and orbital hemorrhages The blood pressure was 135/80 mm Hg

Laboratory investigations Blood urea 440 mg /100 ml serum electrolyte (mEq /L)—sodium 136 potassium 7 5 chloride 85 alkali reserve 14 calcium 4 9 magnesium 3 0 pH (arterial blood) 7 3 hemoglobin 5 1 Gm /100 ml WBC 40 000 per cubic millimeter PCV 20 per cent On September 20 dialysis was performed On September 20 serum potassium was 5 mEq/L and blood urea 330 mg / 100 ml In early October the excretion of urine returned slowly after initial oliguria with heavy albuminuria General condition slowly improved On December 9 the patient was discharged from hospital with blood urea of 117 mg /100 ml and hemoglobin of 9 Gm /100 ml she weighed 38 kilograms (47 5 kilograms prior to snake bite)

In April 1962 the patient came to London after several months of malaise anorexia tiredness occasional vomiting and exertional dyspnea She looked ill and anemic but the only positive abnormal physical finding was slight ankle edema (The blood pressure was 140/70 mm Hg) Laboratory investigations showed that the urine had a specific gravity of 1 005 1 011 and there was slight proteinuria—night volume almost equal to day volume Blood—Hemoglobin 8 2 Gm /100 ml plasma proteins 7 2 Gm /100 ml Serum electrolytes (mEq /L)—sodium 135 potassium 4 5 chloride 103 alkali reserve 20 blood urea 138 mg /100 ml

X ray films revealed contracted calcified kidneys with wavy margins right—10 4 by 4 8 cm left—10 9 by 4 8 cm (normal for women[11]—right 12 1 ± 0 66 cm by 5 9 ± 0 37 cm left 12 8 ± 0 77 cm by 6 1 ± 3 8 cm) The calcification consisted of dense marginal bands with irregular strands running inward toward the renal pelves The strands enclosed a number of irregular translucent areas which were presumed to be deformed pyramids The calcified areas were presumed to represent the remaining renal cortex The renal biopsy specimen was mainly calcific material with a little scarred cortex containing shrunken glomeruli

The patient was discharged from the hospital on August 8 on a low protein high fluid diet plus norethandrolone 10 mg three times a day Symptoms continued but in September 1961 the blood

urea had fallen to 104 mg./100 ml. In February 1962, her weight had returned to normal (47.6 kilograms) and she felt well apart from occasional vomiting. The blood pressure was 140/90 mm. Hg and the specific gravity of the urine was 1.012. Hemoglobin was 10.8 Gm./100 ml. and blood urea was 80 mg./100 ml.

Lloyd Thomas and associates[14] list three biopsy proved examples of cortical necrosis with recovery and in only one case was there renal calcification.[11] A second example is recorded[13] and our case makes a total of three. One other example of snake bite with acute renal failure and dialysis is recorded[16] without mention of renal radiologic appearance. Snake bites are rare in Europeans in Kenya.[17] The venom of the Viperidea consists of a mixture of toxic proteins and enzymes with hemolytic and necrotizing actions. Circulatory collapse, a hemorrhagic state, and local loss of tissue all occur and each of these could have contributed to the renal cortical necrosis.

Five cases of radiologic renal cortical calcification during life are recorded with 2 survivals. Any necrotic tissue may calcify and phosphatase has been detected in the necrotic centers of rabbit pulmonary tubercles.[18] Possibly, phosphatase appears in necrotic renal tissue as a factor in calcification. The kidney is rich in phosphatase.[19] McAlister and Nedelman[13] suggested that 2 months survival is necessary for radiologic calcification to appear. The calcification in the 2 survivors (9 and 19 months) was of patchy distribution. Surprisingly, our patient had extensive diffuse calcification.

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Pigeon atherosclerosis*

While pigeons are usually thought of as nuisances on public buildings and as objects of the affection of park bench sitters, they have many other ways of impinging on the life of human beings. Until recently their scientific use was largely restricted to psychologic experiments (the Seattle World Fair had a number of star performers in learning situations), drug assays, and sources of liver enzymes for biochemists. In 1958, seeking an animal which could be exercised in a reasonable fashion for a study of the effects of exercise in atherosclerosis, we happened upon the spontaneous atherosclerosis which affects the White Carneau pigeon, a time favorite of psychology experimenters.

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handsome bird develops atheroscleros which quite closely resembles the disease that affects man and does so as do human beings while on their natural diet—in the case of the White Carneau a cholesterol free diet. Stimulated by this finding we sampled some other pigeon breeds from among the 100 or more known to pigeon fanciers and found that some breeds have a high prevalence of atherosclerosis others a low. From the latter group we have chosen to work with the Show Racer a bird allied to the homing pigeon of public familiarity but bred for its good looks rather than for it homing ability. The salient features of the disease as we have observed them during the intervening 5 years will be described and the problem which still face us will also be noted.

The White Carneau pigeon hatches after 18 days of incubation and usually has a sibling which hatches at the same time. They are fed by both of their parents initially on pigeon milk a fat rich substance representing the desquamated lining of the parent's crop. This unusual method of feeding the young is somewhat analogous to the production of milk in the human being and the pigeon is the standard test animal for assay of lactogenic hormone. After a week of being fed pigeon milk alone the parents gradually mix solid food with the milk and by 4 to 6 weeks the birds are weaned at which time they have reached almost full adult size and weight. Around 6 months of age they achieve puberty. Their life span is presently unknown. Pigeon have been known to live as long as 30 years and it is probably not uncommon for them to live 15 to 20 years. In our study colony the bulk of the birds are 11 years old having hatched in 1953 a fact established by the presence on their legs of seamless aluminum bands issued by a national pigeon organization and embossed with the year of hatch. These bands are slipped onto the leg at 7 to 10 days of age and cannot be removed thereafter without easily detectable cutting.

At the end of the first week of life about 30 per cent of the White Carneau squabs have microscopic lesions of aortic atherosclerosis the percentage increases to over 70 by 12 weeks of age. The grossly visible atherosclerotic plaques increase in frequency from about 30 per cent at 1 year to 100 per cent at 4 years and older. For 169 pigeons aged 1 through 13 years the mean for the percentage of the thoracic aortic surface covered by plaques is 9 per cent. The lesions themselves are raised yellow to yellow white plaques located most prominently at the distal end of the thoracic aorta where it is likely that the hydraulic stresses exerted on the aortic wall are similar to those which exist at the iliac bifurcation of the human aorta. There are also plaques in the abdominal aorta brachiocephalic iliac renal and carotid arteries. These plaques are subject to the complications which occur in the lesions in human beings such as calcification deposition of hemosiderin ulceration thrombosis hemorrhage and so on. In the coronary arteries the prevalence of atherosclerotic lesions appears to be independent of the occurrence of aortic lesion as is the case in atherosclerosis in human beings at least in the first 2 years of life. The coronary plaques are subject to fewer complications than the aortic lesion on the basis of present information. However an interesting complication of pigeon atherosclerosis has resulted in the death from myocardial infarction of 5 birds making it the second most common single cause of death in our colony. These infarcts resulted from coronary artery embolization by atherosclerotic plaque contents coming from ulcerated plaques in the aortic root which discharged the material into the coronary orifices. The birds which suffered these infarcts were 9 years old in 4 cases and 10 years old in 1 case. It has been mentioned that the life span of the breed is not known so that one cannot postulate how this period of life in the pigeon compares to that in man. In the light of this finding it would seem that pigeon atherosclerosis threatens the life of pigeons albeit by a mechanism different from that in the majority of cases in human beings so far as we know. The aortic lesions produce marked thinning of the aortic wall and aneurysmal formation in the strict sense of that term but thus far we have seen no clinically evident aortic aneurysms. Our guess is that these birds are still too young to have such manifestations.

The Show Racers with a much lower prevalence of atherosclerotic lesions in their aortas have not been so thoroughly studied to date so far as the natural history of their disease is concerned. Difficulties with the supply of the birds are in part responsible for this situation. From what we know at present only about 15 per cent of the bird of this breed have aortic lesions of the type described in the White Carneaux others have fibrous plaques or no plaques at all. The percentage involvement of the aortic surface is less than in the White Carneaux and complications are fewer. Microscopic aortic lesions in young Show Racers are similar to those in the Carneaux but less numerous.

Naturally the biochemical findings in these pigeons were of major interest once the striking nature of the disease and its similarity to the lesions in human beings became evident. A point of major biochemical interest was whether the serum cholesterol level of susceptible pigeons are higher than those of the resistant birds. When one looks at relatively small numbers of birds one gains the impression that serum lipid level are about the same in the two breeds. However as our investigations have been expanded to include large numbers it appears that the susceptible White Carneau pigeons have slightly (but significantly) higher levels in the blood of both cholesterol and triglycerides than do Show Racers. Significant differences in serum lipoprotein patterns in the two breeds have not been detected.

We have investigated in some detail the lipid composition of the atherosclerotic lesions which occur in these pigeons. As is the case in atherosclerosis in human beings the progress of the disease is characterized by increases in cholesterol and cholesterol esters in the lesion with the latter fraction showing the most striking changes. Although the absolute amounts of phospholipid and triglyceride increase as the severity of the disease increases the percentage of the total lipid of the aorta accounted for by these fractions decreases. On the other hand free and ester cholesterol increase both relatively and absolutely.

Our investigations have included studies of the metabolic activity of the pigeon aortas in regard to their ability to synthe ize cholesterol and other lipid From these studies it is clear that the arteries are capable of synthesizing both cholesterol and fatty acids when incubated with C^{14} label d acetate in vitro We could not detect major differences however between susceptible and resistant breeds of pigeons perhaps because *major* differences do not exi t Minor possibly undetectable differences present over long periods of time might lead to the accumulation of lipid in the arteries

The progre s of athero-sclerosis in the e pigeons can to a certain extent be influenced by dietary manipulation Feeding cholesterol even in fairly small amounts increases the severity of the disease in both the aorta and coronary vessels Also from our studies it appears that the level and type of dietary protein can exert at least as great an influence as does the level or type of dietary fat (exclusive of cholesterol) Metabolic studies have provided us with information which suggests that cholesterol feeding accelerates and aggravates the athero clerotic process

The age of the p geon has been hown to be a factor in determining the magnitude of exaggeration of aortic atherosclerosis by cholesterol feeding Very young (4 to 6 weeks old) pigeons develop considerably more aortic athero clero is as a result of dietary cholesterol than do older bird (6 to 7 year old) In contrast however the exaggeration of coronary atherosclerosi is comparable in the two age groups which further suggests the independence of aortic and coronary atherosclerosis in the pigeon

The effect of the early ingestion of pigeon milk on the development of microscopic lesions of aortic atherosclerosis during the early weeks of life has been of considerable interest to us We have shown that the frequency of microscopic aortic atherosclerotic lesions can be markedly reduced among 12 week old squabs by feed ng them a prepared formula which contains no cholesterol from the time of hatch until wean ng although the over all growth of the bird is markedly affected also

We have only recently observed that there i a striking seasonal variation in the prevalence of microscopic aortic atherosclerotic le ion among 12 week-old White Carneau squabs Squabs hatched in the fall have a le ion p evalence of 43 per cent (15 of 35) as opposed to 83 per cent (53 of 64) for squabs hatched in the spring Thi is of particular interest in that it parallel the seasonal variat on in serum cholesterol seen in pigeons Serum cholesterol in p geons i lowest in the fall and highest in the spring

Numerous therapeutic stud es have been made with Whit Carneau p geons (alcohol sitosterol nicotinic acid benzmalecene and safflower o l) Only safflower o l had any therapeutic effect when fed to mature bird and this effect was small

The genetic a pects of pigeon atherosclerosis have been under study and hopefully the availability of large numbers of pigeons with disease and large number with a le er disease prevalence will provide information which has been impossi to obtain in the human subject The obvious (I was done first namely the atherosclerosis- us ceptible White Carneau and resistant Show Racer were cros bred At 2 years of age the prevalences of grossly vi ible aortic lesions in the cros breed (F1 bird) and in each of the parent il lines were all ignificantly different from each other This finding supports the idea that genetic factors play a significant role in pigeon atherosclerosis and further suggests that a polygenic sy tem i the most likely genetic mechani m In a study of the microscopic aortic lesions of 12 week-old birds of each of these types it was noted that although the White Carneaux had roughly the same prevalence of microscopic lesions as of grossly visible lesions at 2 years this was not the case with Show Racers or the F1 bird These findings support the view that the genetic factors re ponsi le for initiation of the microscopic lesions in young birds are largely independent of the factors which lead to their progres ion into gros ly visible plaques in later life

We are currently studying in more detail the lesser degree of atherosclerosis which affects the Show Racer pigeons The mechani m of heredity of the di ease i also under study and presents many problems which result from its probable polygenic background as well as from environmental variables The role of synthesis of plaque components in the arterial wall as opposed to transport into the diseased area from other organs via the blood i being further studied by various techniques The exercise study which furnished the original impetus for using the pigeon has been made but under less than optimal conditions The birds which have a high prevalence of athero-clerosis al o seem to have poor homing ability but we are continuing to investigate Additional studies of myocardial infarction under experimental conditions are pa t the preliminary stages

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Book reviews

CARDIOGRAPHIC TECHNIQUE By A Schott M D (Heidelberg) M R C S and E H Snell A M I E E Second edition London William Heinemann Medical Books Ltd and New York 1963 Grune & Stratton Inc 140 pages Price $4 25

This short manual for cardiological technicians presents in detail much information which should help both technicians and physicians who record electrocardiograms to obtain better and more accurate tracings The chapters which describe the application of electrodes the various leads of the electrocardiogram interference and other artifact and the processing and mounting of the records should be particularly helpful to the technician

A brief history of electrocardiography is given which should prove interesting to the reader In addition the authors present a very simplified explanation of the electrical activity of the heart and the fundamental physical principles of electrocardiography phonocardiography and vectorcardiography Because of the simplicity with which these principles are presented the technician should have no difficulty understanding them This basic knowledge should in turn enable the technician to detect immediately artifacts and errors during the process of obtaining electrocardiogram

Since the authors have covered the problems and difficulties encountered in recording electrocardiograms thoroughly and have described explicitly the proper application and location of limb and chest electrodes which is so important for accurate record this book is recommended as an excellent guide for new technicians and for technician already trained in cardiological techniques as well as for physicians who record their own tracings

GRUNDLAGEN FUR PROPHYLAKTISCHE UND METAPHYLAKTISCHE MASSNAHMEN BEIM HERZINFARKT (Bases for Prophylactic and Metaphylactic Measures in Regard to Myocardial Infarction) By Karl Heinz Straube Rostock Leipzig 1963 VEB Georg Thieme 298 pages Price 48 30DM

This book is mainly a statistical analysis of 1 203 cases of myocardial infarction gathered from several clinics of East Germany Zwickau Rostock Greiswald Stralsund and Wismar Of those 1 203 cases 405 are autopsy cases and 798 clinical cases The interest of the book rests on the large and extensive analytical study All possible parameters are taken into consideration Not less than 260 pages of a dense text plus 38 pages of bibliography and index are necessary for so many comment

Only a part of the basic material is supplied by the University Poliklinik of Rostock where the author is in charge as Oberarzt In spite of the fact the whole series of cases collected is so carefully completed with all necessary data that the views expressed may be considered as issued from one single and compact group Most of these views confirm the statistical conclusion as published by others but many original remarks or suggestions are put forward especially in the field of rehabilitation

In short Straube s book is of real value for all those who are interested in the problem of myocardial infarction as studied in a statistical manner and in regard to all its possible aspects

EAT DRINK AND LOWER YOUR CHOLESTEROL By Frederick T Zugibe Ph D Director Basic Cardiovascular Research Section Veteran Administration Hospital Pittsburgh Pa New York 1963 McGraw Hill Book Company Inc 208 pages Price $4 95

This book is designed as a practical guide for the preparation of diets high in polyunsaturated fat It is written for the layman and the first few chapters are devoted to a discussion of elementary concepts of heart disease and the etiology of atherosclerosis including relationships to the cholesterol problem The scientific information in this book is essentially correct but unfortunately the reader may gain the over all impression that atherosclerosis is primarily related to the levels of cholesterol in the blood

The second and major portion of the book is devoted to the planning of diets and recipes The diets are well formulated and the recipe are easy to follow (the reviewer tried several of them) The taste of the food prepared was not altered appreciably from that of foods cooked with saturated fat Food analysis tables in the appendix provide an easy reference for the fat content of foods The book may be recommended to patients when the physician wishes to advise a diet rich in polyunsaturated fat in the treatment of elevated concentrations of serum cholesterol

OPEN HEART SURGERY FOR MITRAL STENOSIS TECHNIQUE OF OPERATION BY THE LEFT THORACIC APPROACH By H T Nichol M D D I Morse M D G Blanco M D and A Adam M D Hahnemann Medical School and Hospital The Albert Einstein Medical Center Philadelphia Pa Springfield Ill 1963 Charles C Thomas Publisher 66 pages Price $6

The sole purpose of this book is to describe in detail the conduct of direct vision operation for mitral stenosis as practiced by the authors This objective is readily accomplished in a short monograph which is easy to read and understand There is no information in the book concerning the disease entity under consideration This means essentially that the volume will only be of use to thoracic surgeons who intend to personally employ the procedure described

COMPUTER APPLICATIONS IN MEDICINE. By Edward E. Mason, M.D., Ph.D., Professor, Department of Surgery, Ohio State University College of Medicine, and William G. Bulgren, M.S., Graduate Student in Mathematics, Ohio State University. Springfield, Ill., 1963, Charles C Thomas, Publisher. 141 pages. Price $6.75.

This monograph represents an introduction to computer applications in medical research, hospital administration, and clinical practice. No prior knowledge of computational techniques is required for an understanding of the text. Advantages and limitations of computer use are detailed very clearly. The authors draw from a vast experience of their own and that of many others. It is emphasized that in most of these applications one is forced to formulate the problem on hand as precisely as possible. In this respect computer use can become very instructive and educational both for the investigator and clinician. Clear definitions of problems and procedures are a must before automatic means of data processing are considered. In all instances there are stringent requirements for data preparation, choice of analytical procedures, machine programming, and critical evaluation of results. The authors have outlined these basic considerations with great clarity.

Some applications are given in more detail. The cardiologist may take exception to some detail in the introduction to the section on electrocardiography. Some minor inaccuracies in historical detail, however, should not detract from the general quality of the book.

In a fast moving field such as automatic data processing any review may become outmoded in a short time. The field has been covered up to 1962 with an excellent bibliography included. Since complete coverage of the field is practically impossible in a text of this size, the described applications will serve mainly as representative examples. The book can be highly recommended for the reader who wants a first acquaintance with modern computer applications in medicine.

YOUR HEART HAS NINE LIVES. By Alton Blakeslee and Jeremiah Stamler, M.D. New Jersey, 1963, Prentice-Hall, Inc. 263 pages. Price $4.95.

I think that any physician working on the clinical or investigative levels of the coronary artery disease problem would agree that a book by an outstanding science writer such as Alton Blakeslee and a leading authority on atherosclerosis such as Jerry Stamler could hardly fail to be successful. This turns out to be true. Although written for nonmedical readers, it is a book for all men—medical or lay—and their wives.

It is divided into four parts: The Heart in Danger, The Counter Attack, Recovery, Plan for Living. The Introduction was written by Dr. Paul Dudley White.

The concept of the malevolent factors in coronary disease acting in concert is described as the Syndicate—high blood pressure, high serum cholesterol, overweight, excessive eating (especially of certain fats and cholesterol), too little exercise, diabetes, excessive cigarette smoking, tension and stresses, and heredity. There is nothing new here, but in the control of these factors is considered to lie the prevention of atherosclerosis. Thrombosis is not emphasized except as secondary to intimal disruption.

Each of these deadly syndicate members is discussed in very readable style and one comes away with the answer that we lead lives, at least in the United States, which are slothful and gluttonous and hard pressed to a degree that is resented by our metabolic machinery: the result is coronary artery and brain artery degeneration. There are some excellent practical explanation and guidance for patient, and perhaps the best analysis of specific food available. This includes weights, calories, and content of protein, total fat, saturated fatty acids, unsaturated fatty acid, polyunsaturated fatty acids, carbohydrate, and cholesterol in everything from a drink called "Grasshopper" to gefullte fish.

With Dr. White I must say that instead of skimming the pages I read the whole book. It is full of good science and is a "safe" and not alarming book to recommend to patients.

There is an ancient Persian proverb that says that the two greatest dangers for an older man are a good cook and a young wife. The authors seem to think that the good cook is the more deadly, but they also warn the newlyweds where the wife and the cook are combined. "Many a young bride sets out to kill her husband—unwittingly—with the food she sets before him." Our present knowledge indicates that prevention of atherosclerosis probably should begin in childhood and this book is wisely pointing the way.

PATHOGENESIS OF ESSENTIAL HYPERTENSION. Proceedings of the Prague Symposium 1960. Edited by J. H. Cort, V. Fencl, Z. Hejl, and J. Jirka of the Institute for Cardiovascular Research, Prague, Czechoslovakia. New York, 1962, The Macmillan Company. 477 pages. Price $15.

It is regrettable that the advances in our understanding of essential hypertension since 1960 have not made this book obsolete. Instead I find that this is one of the better presentations of the neurogenic and psychogenic components of regulation of blood pressure.

Zanchetti's description of the effect of the pressor receptors upon sham rage should be of equal interest to physicians with psychosomatic orientation and those with somatopsychic leanings. Folkow and Brod's work together gives a clear picture of neurogenic control of blood pressure and its possible relationship to the genesis of hypertension.

The prolix Russian contributors tended to report views more than data, although Miasnikov's report of increased blood pressure in switchboard operators is of considerable interest and should offer a field of study.

Pickering offers a clear statement of his quantitative approach to hypertension. It is unfortunate that a set rebuttal was not planned for the many disapproving comments carry some heat but little ordered light. Sir George emerges the victor, but I regret that the opposing forces were not better prepared.

Amine metabolism, renal factors, changes in vessel walls, and epidemiological aspects were also considered. Most of these aspects are now a bit dated.

In summary, I would suggest this volume is required reading for all investigators of hypertension, and I think that rapid reading of it will be enjoyable to most cardiologists. To all concerned with biologic investigation, I recommend Peterson's elegant paragraph on page 736 on hypothesis, model formulation, and quantitative data. It should not be hidden in the midst of a fading conference report.

THE PATHOLOGY OF THE PULMONARY VASCULATURE. By C. A. Wagenvoort, M.D., Donald Heath, M.D., and Jesse E. Edwards, M.D. Springfield, Ill., 1963, Charles C Thomas, Publisher. 494 pages. Price *$25.50*.

This is a very good book and one that is much needed today with the ever-increasing interest in pulmonary heart disease and pulmonary vascular disease. The monograph has many very good illustrations, including a few electron microscopic ones. The authors discuss the normal pulmonary vasculature in the fetus, infants, and children, as well as adults. Greatest emphasis is placed upon congenital heart disease, although other diseases are discussed as well. Each chapter is documented with many references. Unfortunately, the problems are so extensive that a *complete or encyclopedic presentation of the* subject is impossible. Nevertheless, this is a good reference book and is recommended to all physicians and students who are interested in various aspects of the pathology of the pulmonary blood vessels.

NEW IDEAS ON REHABILITATION. Report of a Study Day on Facilities for Education, Rehabilitation and Care Services Held in London, June 1963. The Chest and Heart Association, Tavistock House, North Tavistock Square, London, W. C. 1, England, 1963. Printed by Waterlow & Sons Ltd. 102 pages. *Price $2.50*.

This small volume consists of brief presentations by 16 authorities in the various disciplines—medical and paramedical, representing official and voluntary health agencies—dealing with the rehabilitation of patients with respiratory and cardiovascular disorders. Readers in the U.S.A. will note many similarities to their own experience *in motivational and placement problems* and in the techniques directed toward their solution. Some of the methods described are, of course, applicable only in the British system of medical practice. The discussants appear to be exceedingly well qualified, and the clarity of expression in their presentations is noteworthy.

ELECTROCARDIOGRAPHIC NOTEBOOK. By Irené Ferrer, M.D., Associate Professor of Clinical Medicine, Columbia University College of Physicians, New York, N. Y. Ed. 2. New York, 1964, Hoeber Medical Division, Harper and Row. 112 pages. Price $7.75.

This little notebook of a little over 100 pages which is small enough to fit into one's coat pocket should be of value to students and members of house staffs. Obviously, such a book cannot be complete, but it does discuss some of the most common clinical electrocardiographic problems. When used as a supplement to more complete presentations, it should be of value to beginners.

Announcement

THE ANNUAL SYMPOSIUM OF THE MEDICAL STAFF OF THE MEMORIAL HOSPITAL OF LONG BEACH will be held at The Memorial Hospital of Long Beach on Wednesday, May 20, 1964.

The program will feature papers by staff physicians of Memorial Hospital. Also participating will be Robert C. Horn, M.D., Director of the Department of Pathology, Henry Ford Hospital, Detroit, Mich.

Additional information is available from George N. Trimble, M.D., Symposium Secretary, The Memorial Hospital of Long Beach, 2801 Atlantic Ave., Long Beach 6, Calif.

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Editorial

Viral endocarditis

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It is widely believed, even among cardiologists, that viral endocarditis does not exist. It has been stated that neither endocarditis nor valvulitis has been recognized during acute viral infections and that chronic valvular disease has not been observed as a sequel. Nevertheless, Kirschner[1] in 1931 reported instances of myocarditis after rubella, variola, and influenza infections. More recently, Tedeschi and Stevenson[2] observed 2 children with interstitial myocarditis in whom the endocardium was found to be involved in the inflammatory process. They suggested that a revision of the belief that endocardium and epicardium are spared in so-called interstitial myocarditis was indicated. Since 1951 it has become recognized that many instances of "interstitial" or "idiopathic" myocarditis are viral in origin and are due in particular to Coxsackie Group B infections. In 1954 Cookson[3] described a 60-year-old woman who was in perfect health until she developed a biphasic febrile illness associated with pneumonitis and progressive cardiac enlargement. Viral infection was considered but not proved to be the etiology. At necropsy, the aortic valve was almost totally destroyed, there were no verrucae on the valve, and the other valves appeared to be normal.

Viral endocarditis may be more common than the few reports in the literature would indicate. It is difficult to believe that of all the viruses which infect man none are endocardiotropic. If such is the case, it would be important to know what it is about the endocardium that protects it from viral infection. However, it is much more likely that many instances of viral endocarditis are overlooked. Viral myocarditis, especially in infants and children, may be a fulminating disease. The presence of an associated nonverrucous viral endocarditis may go undetected unless the valves are routinely sectioned at necropsy. The fact that the disease is usually of short duration would preclude verrucous formation or valvular deformity. On the other hand, if the patient survives, residual valve deformity diagnosed clinically or pathologically at some future time may well be considered to be the residual of rheumatic carditis.

Although strong clinical evidence for viral endocarditis is lacking, it has been well established experimentally that certain viruses may produce valvulitis. Lou and associates[4] inoculated cynomolgus monkeys with Group B, type 4 Coxsackie virus recovered from the heart of a 10 day old infant who died from encephalomyelitis, myocarditis, hepatitis, and pancreatitis. Of the 9 monkeys inoculated, the virus was isolated from the heart in 6, whereas in 8 monkeys myocarditis was considered to be present on the basis of microscopic examination of the heart. Of particular interest is the fact that acute valvulitis was observed in 2 monkeys. The valve tissue in these monkeys was edematous and infiltrated by inflammatory cells, and the overlying endothelium was swollen. No verrucae were present.

Kilham, Mason, and Davies showed that infection of mongooses with encephalomyocarditis virus resulted in acute endocarditis and valvulitis in addition to myocarditis.

Finally, Pearce[8] demonstrated that inoculation of rabbits with Virus III resulted in valvulitis with thickening of the valve leaflets and at times also the chordae tendineae. Because Virus III infection is associated with typical inclusion bodies, there could be no doubt of the viral etiology of the valvulitis in the experiments conducted by Pearce.

Thus there is ample evidence to indicate that viruses may produce valvulitis in experimental animals. There is also extensive clinical evidence to indicate that viruses may produce pericarditis and myocarditis in man. Viral endocarditis is yet to be firmly established as a clinical entity in man, but certain clinical facts, in addition to those already presented, support the idea that viruses may produce endocarditis and/or valvulitis in man. When a patient exhibits clinical and laboratory manifestations of aortic or mitral valvular disease and the etiology of the valvular disease cannot be ascribed to syphilis, bacterial endocarditis, arteriosclerosis, or congenital heart disease, the lesion is usually considered to be rheumatic in origin whether or not the patient presents a history of previous episodes of carditis, polyarthritis, chorea, erythema marginatum, or subcutaneous nodules. The failure to obtain a history of acute rheumatic fever is usually considered to be due to the fact that the patient is either a poor historian or the clinical manifestations of the acute episodes of rheumatic fever were so mild that they were ignored. Unfortunately, the clinician is usually not disturbed by the absence of a history of acute rheumatic fever because he knows that the clinical signs of valvular disease after an acute episode of rheumatic carditis may be delayed 10 or more years. He is also aware of the fact that in tropical or subtropical climates a "smouldering" form of rheumatic fever exists in which valvular disease develops without clinical manifestation of acute rheumatic fever. Thus the physician often considers it justifiable to make a diagnosis of rheumatic valvular disease in the absence of a history of acute rheumatic fever. In essence, the diagnosis of rheumatic valvulitis is often one of exclusion.

A little more difficult to explain is the absence of the rheumatic nodule (Aschoff body) in about 30 per cent of patients who are considered to have typical old or healed rheumatic valvulitis at autopsy.[9] Although it is acceptable to consider rheumatic fever as the cause of aortic and mitral valve lesions in many patients without a previous history of rheumatic fever, obviously, if cardiology is to progress, other possibilities should be searched for. One of the possibilities is viral infection of the endocardium. If in the course of Coxsackie viral myocarditis in man valve lesions occur similar to those described by Lou and associates in cynomolgus monkeys, then it would be expected that in some instances residual scarring of the valves may occur. On subsequent physical examination, the clinical manifestations of a residual fibrotic valve lesion may be attributed to rheumatic carditis for lack of a better diagnosis. There is a need for careful study of the endocardium, including the valves, in unexplained instances of valvular disease, especially if Aschoff bodies are not found in the myocardium. Such studies should include, in addition to histologic examination, attempts at isolation of the virus, histochemistry, and electron microscopy. The recent observation that children with endocardial fibroelastosis have significant

skin reactivity to mumps antigen is further evidence that viruses may produce endocardial disease.[9]

There are several forms of endocarditis which are poorly understood, including nonbacterial verrucous endocarditis, congenital (fetal) valvular endocarditis, and endocarditis attributed to toxins. It is quite possible that in some instances these endocarditides are viral in etiology. There is a need to study the possible relationship between viral disease and endocarditis using modern techniques in order to either establish or eliminate viral endocarditis as a disease entity. Certainly if acute or chronic viral valvular endocarditis does exist, it would help to explain the not uncommon clinical dilemma of valvular disease for which no positive etiology is readily apparent, a dilemma which has often been solved by clinical empiricism.

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Clinical communications

Observations in patients with implanted pacemaker

II. Effective refractory period and full recovery time of the ventricular myocardium calculated from clinical tracings

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Introduction of an internal pacemaker has made it possible to investigate excitability of the heart muscle in man. In patients in whom wires lead from the myocardium to the surface of the body, connection can be made with a physiologic stimulator which allows one to choose the basic heart rate and to vary both the strength and incidence of the electrical stimuli.[1-4] Another group of studies can be undertaken in patients with implanted pacemaker[5-8] in whom sinus rhythm with full A-V conduction represents the dominant rhythm while the pacemaker stimuli compete with the sinus excitations and cause premature ventricular beats or fusion beats when they fall outside the refractory period. In such cases the refractory period can be calculated from long tracings which show a multitude of responses to pacemaker stimuli in varying intervals from the sinus mechanism. When clinical tracings are used, neither the rate of the basic rhythm nor the strength of the electrical stimuli can be varied at will. On the other hand, clinical studies may be made repeatedly without inconvenience to the patient. They allow long-range observations which are precluded by the danger of infection when the wires leading from the myocardium are exposed at the surface of the body.

Material and methods

During the past 2 years, 35 patients suffering from Adams-Stokes attacks were treated with implanted pacemakers in the Maimonides Hospital. In 11 with intermittent A-V block the pacemaker stimuli combined with the fully conducted sinus excitations to form a ventricular parasystole. The General Electric Kantrowitz pacemaker which was used in our patients has the advantage of permitting variations in the rate of pacing by employment of an external control unit.[8] In this way, one is able to choose a rate that will result in slight increments in the intervals between sinus mechanism and electrical stimuli in successive beats. The longest distance then, which is not followed by a response to the pacemaker stimulus (Fig. 1) is a measure of what Lewis and Drury have termed the "effective refractory period."[9,10]

The General Electric pacemaker delivers impulses of 2 millisecond duration. The energy output per impulse is 64 microjoules.[8] The threshold energy requirement for stimulation of the ventricle was calculated in a patient whose electrode wires pierced the skin. It was [illegible] microjoules one day after insertion of the myocardial electrodes.[11] Thus, the energy output was about 8 times the threshold value in the early stage of application of an internal

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pacemaker. In the weeks following insertion, however, the myocardial electrodes cause an inflammatory reaction which progresses to formation of scar tissue. The concomitant increase in patient resistance[1] results in reduction of energy per impulse at the site of the electrodes. The process levels off about 3 weeks after insertion of the electrodes.[1] In one of our patients whose electrode wires pierced the skin, it was shown 6 months after insertion of the myocardial electrodes that threshold requirement had increased to 15 microjoules, that is, one fourth of the output delivered by the General Electric pacemaker.[8]

Results

Table I shows the figures for the effective refractory period which were calculated in 41 determinations carried out in 11 patients. The duration of the refractory period varies from 220 to 390 msec. Such variations depend on three factors: (a) spontaneous fluctuations, (b) duration of the ventricular cycle of the basic rhythm, and (c) time which has elapsed since insertion of the myocardial electrodes. Table I lists the intervals between the date of implantation and the time when the study was made, as well as the range and mean values of cycle length of the basic rhythm. The effect of cycle length on the refractory state was calculated in 5 cases. When the cycle length decreased, the mean reduction in the length of the refractory period amounted to 10.2 per cent of the decrease, ranging from 8.3 to 15 per cent. It seems that the percentage changes rapidly with marked variations in cycle length. More studies will be required to obtain dependable information on this point.

Table II lists variations in the length of the refractory period in correlation with time elapsed after insertion of the electrodes in the myocardium. Section *A* of Table II shows the figures for the refractory period during the first week after implantation. The mean value is 267 msec. for a mean cycle length of 713 msec. Among [illegible] cases studied, Cases 7 and 8 are outstanding in that they show unusual duration of refractoriness, namely, 365 and 340 msec., respectively. In the other cases (Cases 1 the range of refractoriness is from 220 to 295 msec., and the mean value is 253 msec. Variations in the duration of the refractory period are determined by spontaneous fluctuations rather than by the length of the basic ventricular cycle. In Case 3b, for instance, the refractory period measures 295 msec. for a cycle length of 670 msec.; in other cases (Cases 1abc, 2abc, and 5a) the refractory period is shorter, although the duration of the ventricular cycle is considerably longer. On the other hand, when several measurements were made in a single case on the same day, a remarkable constancy of the refractory period was sometimes noted. For instance, in Case 2, three measurements (a,b,c) yielded exactly the same figure of refractoriness.

The duration of the refractory period generally increased progressively during the first 3 weeks after implantation. Section *B* of Table II shows measurements which were obtained in the second week. Eight determinations were performed in 6 patients. The duration of the effective refractory period ranged from 295 to 365 msec.; its mean value was 326 msec. for a mean cycle length of 777 msec. Thus, the refractory period has increased from 267 to 326 msec. in the second week after implantation. This increase is out of proportion to the increment in cycle length, which is but 64 msec.

Section *C* of Table II shows measurements of the refractory period made during the third week after implantation of the pacemaker and later. The range is from 280 to 390 msec.; the mean value is 329 msec. The corresponding mean cycle length of 714 msec. is considerably shorter than that observed during the second week (777 msec.). Obviously, increase in the refractory period would have been even more conspicuous had the mean cycle length remained the same as in the second week.

In Case 10 the duration of the refractory period determined on the twenty-seventh day after implantation (Table I, Case 10b) was 280 msec. for a mean cycle length of 700 msec. The measurement was repeated on the thirty-third day (Case 10c) after the patient had been treated with quinidine. The effective refractory period was then 350 msec., whereas the cycle

Table I. Duration of refractory period and full recovery time

Case		Days after implantation	Effective refractory period (msec.)	Full recovery time (msec.)	Cycle length (msec.) Range	Mean
1 M I	a	3	260	370	710-760	735
	b	6	245	315	630-870	715
	c	7	260	315	760-800	780
	d	13	300	320	720-870	795
	e	14	305	370	700-760	730
	f	32	335	--	730-820	775
	g	4 mo.	320	-	740-820	780
2 S B	a	1	245	275	760-800	780
	b	1	245	270	760-800	780
		1	245		760-800	780
	1	1	270	Not enough beats	520-540	530
3 T W	a	2	235	300	570-610	590
	b	4	295	345	650-690	670
4 Y S	a	Catheter electrode in right ventricular cavity	360	-	840-900	870
	b	2	285	335	590-650	620
5 P I	a	2	255	305	810-870	840
	b	8	a 365	380	820-920	870
			b 340	345	560-600	580
F R	a	2	245	295	660-690	675
	b	9	305	325	800-840	820
	c	21	320	---	720-760	740
	d	3 mo.	315	330	820-870	845
J H		1	365	375	680-730	705
M A	a	3	340	380	700-760	730
	b	10	360	420	820-880	850
		11	350	400	740-840	790
	d	20	380	415	760-820	790
	e	27	360	395	710-760	735
	f	29	a 390	410	720-760	740
			b 365			570
9 M S	a	8	295	330	680-740	710
	b	29	330	---	560-580	570
	c	34	315	---	560-620	590
	d	35	315	---	570-580	550
	e	62 mo.	335	---	740-800	770
10 P B	a	2	300	---	660-700	680
	b	27	a 265	---	500-540	520
			b 280	---	680-720	700
	c	33	350	---	670-720	690
	d	41	290	---	700-760	730
11 F H		14	320	355	640-700	670

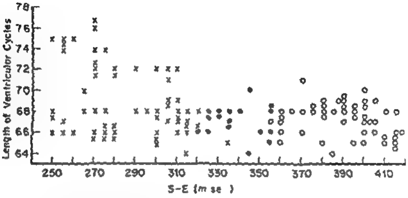
After administration of quinidine.

Table II *Duration of refractory period and full recovery time in relation to time after implantation*

Case		Days after implantation	Effective refractory period (msec)	Full recovery time (msec)	Cycle length (msec) Range	Mean
A Refractory period and full recovery time in the first week after implantation						
1 M I	a	3	260	370	710–760	735
	b	6	245	315	730–820	775
	c	7	260	315	[illegible]60–800	780
2 S B	a	1	245	[illegible]	760–800	780
	b	1	245	[illegible]	760–800	780
	c	1	245		760–800	780
	d	1	230	—	520–540	530
3 L W	a	2	235	300	5[illegible]0–610	590
	b	4	295	345	650–690	670
4 V S		2	295	33[illegible]	590–650	620
5 R L	a	2	255	305	810–870	840
6 R R	a	2	245	[illegible]	660–690	675
7 J H		1	305	3[illegible]5	580–730	705
8 M V	a	3	340	390	[illegible]00–760	730
B In the second week after implantation						
1 M L	d	13	300	3[illegible]0	[illegible]20–820	[illegible]75
	e	14	305	320	700–760	730
5 R L	b	8	365	380	820–920	870
6 R R	b	9	305	325	800–840	820
8 M V	c	10	360	420	820–890	850
	d	11	350	400	740–840	790
9 M S	a	8	295	330	680–740	710
11 F H		14	320	355	640–700	670
C In the third week after implantation and later						
1 M I	f	32	335	—	[illegible]30–820	775
	g	7 mo	320	—	740–820	780
6 R R	c	21	320	—	720–760	740
	d	3 mo	315	330	820–870	845
8 M V	d	20	380	415	[illegible]60–820	[illegible]90
	e	22	360	395	710–760	735
	f	29	390	410	720–760	740
9 M S	b	29	330	—	560–580	570
	c	34	315	—	560–620	590
	d	35	315	—	520–580	550
	e	6[illegible] mo	335	—	[illegible]40–800	770
10 J H	a	22	300	—	660–770	[illegible]80
	b	27	280	—	[illegible]	[illegible]
	c	41				

had decreased to 670 msec. A depressive action by quinidine upon the refractory period has been observed in the experimental animal.[9,10]

Electrical stimuli which fall early after the end of the refractory period elicit a response with considerable delay. This was observed both in the experimental animal[10]



S-E Interval between sinus beat and electric stimulus
X Electric stimulus ineffective
● Electric stimulus effective with latency
○ Electric stimulus effective without latency

Fig. 1. The ordinate measures the length of the basic ventricular cycles (in one hundredths of a second). The abscissa the distance between sinus mechanism and electrical stimulus (S-E interval) in milliseconds. Electrical stimuli which are ineffective because they fall into the refractory period are indicated by X; those stimuli which elicit responses with conspicuous latency are indicated by closed circles; others which are effective without noticeable latency are shown by open circles. The longest S-E interval without response indicates the length of the effective refractory period; it measures 320 msec. The full recovery time marked by response with minimal latency measures 355 msec. The length of ventricular cycles which precede effective electrical stimuli ranges from 0.64 to 0.70 second.

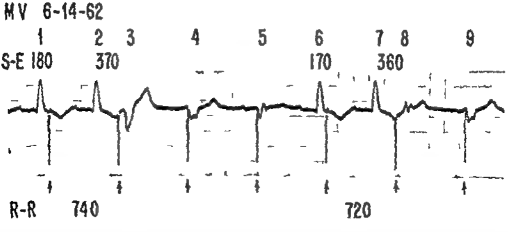


Fig. 2. The basic rhythm is formed by sinus beats which are conducted to the ventricle (1, 2, 6, 7). The electrical stimuli (*indicated by arrows*) are effective only when they fall outside the refractory period. S-E indicates the time between sinus mechanism and electrical impulse. Some electrical stimuli arrive late in diastole and elicit responses (4, 9) without conspicuous delay. Others which fall early produce responses (3, 8) with a latency which measures approximately 80 msec. Their ventricular complexes show marked aberration in shape as compared with beats 4 and 9. The fifth beat is obviously a fusion beat.

and in clinical studies.[4, 6] The factors responsible for the phenomenon of latency were studied by Hoffman and associates[13] and explained in this way.[14] The time required for the local response to rise to an effective level varies with both the strength of the stimulus and the level of membrane potential during phase 3. Second, the rate of rise and amplitude of the resulting action potential vary and thus influence the rate at which activity spreads in the immediate vicinity of the stimulating electrode. With advancing diastole latency diminishes. When the point of full recovery is reached the interval between the electrical stimulus and ventricular response becomes constant. Drury[19] advocated the use of the interval between the first response with latency to the point at which latency does not show further change for estimation of the full recovery time. He emphasized that this time was constant from one animal to another of the same species and serves as a more dependable means of comparison of excitability than does the refractory period.

Fig. 2 shows electrical stimuli which arrive late in diastole (4, 9) and elicit responses without conspicuous delay. Other stimuli (3, 5) which arrive early produce ventricular contractions after a considerable latency. Their ventricular complexes show marked aberration in shape, such as has been observed by others.[4, 6]

In Fig. 3 eight strips of a single tracing which exhibit premature ventricular contractions in response to electrical stimuli are so arranged that the interval between the sinus mechanism and electrical stimulation (S-E interval) steadily increases. It can be seen that those with the shortest S-E interval show the longest latency. In the last strip, in which the electrical stimulus falls after the longest interval (S-E

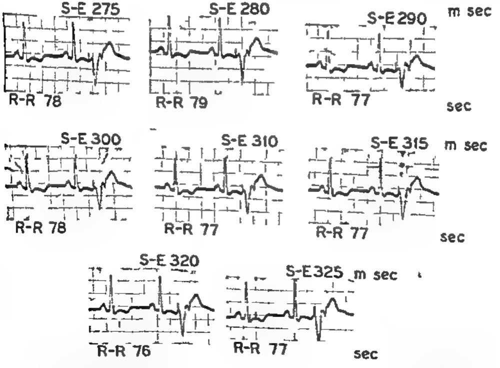


Fig. 3. Regular sinus rhythm is interrupted by premature beats which are responses to electrical stimuli. Eight strips of a single tracing are so arranged that the interval between sinus mechanism and electrical stimulus (*S-E*) progressively increases. Those premature beats with the shortest S-E interval (*in the top row*) show the longest latency. In the last strip, in which the S-E interval is 325 msec., there is no more conspicuous latency. The full recovery time lies between 320 and 325 msec. Inverted P waves which follow each premature beat indicate that the electrical impulse is conducted to the atria.

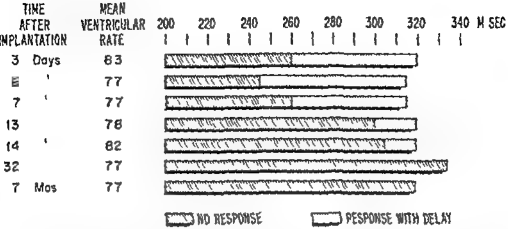


Fig. 4. Case 1. Seven determinations of the phases of excitability, each indicated by a horizontal bar, were made between the third day and 7 months after implantation. *The effective refractory period is indicated by oblique hatching, the recovery phase by dots. The intervals between sinus* mechanism and electrical stimulus are indicated in milliseconds above the bars. During the first week the measurements remain fairly constant, except for a slight spontaneous shortening of the effective refractory period which occurs on the sixth day. In the second week (on the thirteenth and fourteenth days) the effective refractory period has increased from 260 to 305 msec., although the basic ventricular rate has somewhat increased; the full recovery time, however, remained constant. Measurements taken on the thirty-second day and 7 months after implantation, respectively, revealed a further increase in the duration of the effective refractory period, and a recovery phase was no longer noticeable.

325 msec.) there is no more conspicuous latency. Thus, the full recovery time lies between S-E 320 and 325 msec.

The duration of the full recovery time as observed in our studies is listed in Tables I and II. Table II shows the figures correlated with the time intervals after implantation. During the first week 12 determinations were made in 8 patients. The full recovery time ranges from 270 to 380 msec.; the mean value is 319 msec. for a mean cycle length of 725 msec. Variations in the full recovery time which are independent of cycle length are noted. For instance, in Cases 3a and 5 recovery times are nearly identical, whereas cycle length differs by as much as 250 msec.

When the figures for the mean effective refractory period are subtracted from the mean full recovery time, the difference is 46 msec. for the first week after implantation. In the second week the difference is reduced to 30 msec., and afterward it is zero in 10 out of 14 determinations. This means that during the first 3 weeks the effective refractory period steadily increases at the expense of the full recovery phase until at the end the latter is abolished in most of the cases. This fact is illustrated in Fig. 4 (Case 1), in which the length of the refractory period is indicated by hatching, the recovery phase by dots. Seven determinations were made between the third day and 7 months after implantation. The measurements remain fairly constant in the first week, except for a spontaneous, transient shortening of the refractory period which is noticed on the sixth day after implantation. In the second week a progressive increase in the effective refractory period with corresponding decrease in the recovery phase has occurred. The last two determinations, made 32 days and 7 months, respectively, after implantation, no longer show a recovery phase.

Comment

Employment of the internal pacemaker on a larger scale in the future will open a wide field for studies of myocardial excitability. This is facilitated by the possibility of using clinical tracings which exhibit a ventricular parasystole like that observed in about one third of our cases with the implanted pacemaker.

The figures which we obtained in measuring the duration of the refractory period

are in fair agreement with those reported by others Lewis and associates [1] who using a physiologic stimulator sent electrical impulses to the endocardial surface of the right ventricle obtained figures ranging from 250 to 300 msec Their report did not mention the length of the basic ventricular cycles Our studies revealed sometimes a remarkable constancy of measurements when they were made on the same day or on successive days (Table II Case 2abc) The figures of course vary with changes in cycle length In 5 cases we calculated the effect of variations in cycle length upon the duration of the refractory period An increase in cycle length caused an increase in the refractory period which on the average amounted to 10 per cent of the prolongation of the basic ventricular period This percentage seems to diminish rapidly with abrupt increase in the rate of the basic rhythm Moreover conspicuous spontaneous fluctuations in refractoriness were observed in both the experimental animal[10,15] and man They are disturbing in calculations of the phases of excitability since they result in overlapping (see Fig 1) so that the boundaries are more often than not marked by a transitional zone rather than a sharp line

It is known that the Q T interval does not exactly coincide with the duration of the effective refractory period In our experience refractoriness ends at the nadir of the T wave and the first electrical stimulus which elicits a response lies usually about 20 msec after the nadir of the T wave Following the example of Drury [16] we used the full recovery time that is the end of the phase of ventricular responses with diminishing latency as a measure or relative refractoriness Others have employed instead[6] or as an interchangeable measurement[4] the phase of ventricular responses with varying aberration of the shape of the ventricular complexes It must be borne in mind that in determining latency one has to be sure that during the interval between the electrical stimulus and response the tracing follows exactly the same course that it would without intercession of a premature ventricular beat Marked aberration of the shape of the ventricular response leads readily to errors in determination of latency Moreover in our experience the phases of diminishing latency and varying shape of the ventricular responses do not concur the former are usually shorter than the latter

When the phases of excitability are studied for several weeks after the implantation of a pacemaker a steady increase in the effective refractory period can be observed which is clearly at the expense of the recovery phase This phenomenon is explained by an increase in patient resistance [13] which occurs during the first 3 weeks because of tissue reaction at the site of the electrodes The concurrent diminution in impulse power is responsible for prolongation of the effective refractory phase which encroaches upon the period of recovery Therefore a period of recovery was only exceptionally manifest in determinations of myocardial excitability which were made during the third week after implantation of a pacemaker or in later stages These facts offer an explanation for puzzling observations reported by Burchell [4] who noticed in his Case 2 a prolongation of the refractory period which followed administration of reserpine but could not be reproduced in later stages

It was not surprising that administration of quinidine (in Case 10) caused a prolongation of the effective refractory period In Case 4 determinations of refractoriness were made first with the electrodes at the endocardial surface of the right ventricle and later with the electrodes in the wall of the left ventricle The earlier determination yielded a longer refractory period than did the second study Moore [17] working on the canine heart has pointed out that the endocardial cells show a longer functional refractory period than that of the epicardial units when studied at physiologic rates Another factor which may have been responsible for prolongation of the refractory period at the time when venous electrodes were used could have been shifting of the electrode away from the endocardium which results in diminished current density at the site of myocardial stimulation A supernormal phase of excitability which was demonstrated by Soloff[3] and Linenthal and Zoll[4] was not observed in our studies presumably because our pacemaker delivers

stimuli which were much above threshold values Feldman[2] who used an arrangement which allowed him to employ stimuli far below threshold values was likewise unable to show the presence of a supernormal phase

Summary

Excitability of the ventricular myocardium was studied in 41 clinical electrocardiograms of 11 patients who after implantation of a pacemaker presented sinus rhythm with full conduction in competition with the electrical stimuli (parasystole)

The duration of the effective refractory period and full recovery time was determined for varying lengths of the basic ventricular cycle For measurements of the full recovery time the parameter of diminishing latency of responses was employed following the example of Drury Aberrancy of ventricular responses which was used by others may yield figures indicative of an unduly long duration of relative refractoriness

The effective refractory period grew steadily longer in measurements made during the first 3 weeks after implantation that is during the time of tissue reaction and formation of scar tissue at the site of the electrodes This results in diminishing strength of the electrical stimuli hence the effective refractory period becomes longer and encroaches upon the phase of recovery After the second week a period of recovery was no longer noticeable in most of our cases

Variations in the duration of refractoriness are due to varying length of the basic ventricular cycle Moreover there are conspicuous spontaneous fluctuations which lead to overlapping of the phases of refractoriness so that their boundaries are often indicated by a transitional zone up to 15 msec wide rather than by a sharp line

In one case in which quinidine was administered a prolongation of the effective refractory period was observed In another case in which measurements of excitability were made with the electrode at the endocardial surface of the right ventricle the figures for the effective refractory period were higher than in later determinations when electrodes which rested in the myocardial wall were used

We wish to express our gratitude to Dr B F Hoffman who gave much of his time in discussing problems and offering helpful advice and criticism

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The pulmonary vascular volume in man. Measurement from atrial dilution curves

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Measurement in living man of the volume of blood in the vascular bed of the lungs is possible from knowledge of the blood flow through the lungs and of the transit time of an indicator from pulmonary artery to pulmonary vein. Although direct measurement of that transit time has not been reported, indirect estimates have been made by Milnor and associates[1] and by Dock and associates,[2] as the difference between transit times from pulmonary artery to peripheral artery and from left atrium to peripheral artery.

Theoretically, it is possible to measure pulmonary blood volume by sampling from the left atrium after injection into the pulmonary artery. This measurement offers the evident advantages of simplicity and possible reduction in error, since only a single dilution curve is involved. Therefore, an investigation of this technique was undertaken.

Materials and methods

Fifteen measurements of the blood volume from main pulmonary artery to left atrium (hereafter referred to as pulmonary blood volume) were obtained in 10 patients in whom diagnostic evaluation necessitated catheterization of the left side of the heart.

All patients were adults with hemodynamically significant rheumatic heart disease. Four patients had isolated mitral valve disease, 4 had isolated aortic valve disease, and 2 had severe or moderately severe lesions at both valves. Although several had a history of cardiac decompensation in the remote past, all were clinically compensated at the time of study.

All patients were studied in the fasting state, under mild barbiturate sedation, at rest in the supine position. Under local procaine analgesia, a Goodale-Lubin catheter was introduced through a right median antecubital vein, into the main pulmonary artery, and a Brockenbrough catheter by transseptal technique[3] into the left atrium. For the recording of an arterial dilution curve simultaneous with the atrial curve, a Cournand needle was inserted into a brachial or femoral artery, or a catheter

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was introduced into the aortic root from the right brachial artery. Immediately after appropriate pressures and gradients had been recorded, the dilution studies were performed.

At a prearranged signal 6.6 mg. of indocyanine green dye in 1 ml. of diluent and a saline flush were injected rapidly into the pulmonary artery from a calibrated pipette.[4] The duration of injection of dye and flush were recorded and the mid point of injection of the dye was obtained from knowledge of the volumes of catheter, dye injectate, and saline flush. This mid point was taken as zero time. By means of Harvard pumps, blood was withdrawn through Gilford densitometers at a constant rate of 0.7 ml. per second from the left atrium and the arterial collection site. The outputs of the densitometers were recorded on a photographic recorder (Electronics for Medicine). Calibration was by the integrated sample technique.[5] Hematocrit was determined in duplicate by the microhematocrit technique[6] without correction for trapped plasma. Curves were plotted semilogarithmically and extrapolated to 1 per cent of peak concentration. Cardiac output was calculated for each arterial dilution curve and cardiac output and mean transit time were calculated for each left atrial curve by the usual Stewart-Hamilton formulas.[7,8] The mean transit time was corrected for the delay introduced by the sampling system,[9] including catheter and densitometer cuvette. In 13 experiments both the left atrial and the arterial dilution curves were satisfactory, and the mean of the flows calculated from the two curves was used as cardiac output. In 2 experiments the arterial curves were unsatisfactory, and cardiac output was measured from the atrial dilution curve alone. The volume of blood between pulmonary artery and left atrium was calculated as the product of cardiac output and pulmonary mean transit time.

The results of the study were analyzed by conventional statistical techniques, the product moment correlation coefficient (r) and Student's t test. The latter was also used to compare the pulmonary blood volumes obtained in this study with those reported by previous authors.

Results

The results of the study are listed in Table I.

Left atrial dilution curves. In all experiments satisfactory dilution curves were obtained from the left atrium. Fig. 1 is representative of the data of the entire series. In each instance, the downslope of the aortic or arterial curve was slower than that of the atrial curve, consistent with the additional mixing to which dye was subjected between the two sampling sites. In no instance was there difficulty in selecting the exponential downslope.

Cardiac output. Cardiac outputs calculated from the atrial dilution curves agreed with those calculated from simultaneous aortic or peripheral arterial dilution curves. Fig. 2 shows the excellent correlation between the two flow measurements. There was, however, a small but systemic difference between paired measurements. Outputs from atrial curves were slightly higher (mean difference = 0.12 L. per minute) than those from aortic curves. The discrepancy was somewhat greater (mean difference = 0.27 L./min.) when the sampling sites were atrium and peripheral artery. When the entire series is evaluated, cardiac outputs from left atrial curves exceeded those from downstream curves by a mean difference of 0.19 L./min. ($p < 0.05$). The difference, although statistically significant and of interest, is small and of negligible influence in the calculation of central blood volumes. In this series, for example, the use of the output calculated from the atrial curve in place of the mean of the outputs calculated from atrial and downstream curves alters mean pulmonary blood volume by only 3 ml./M.[2] or 1 per cent.

Pulmonary blood volume. The mean pulmonary blood volume ranged from 236 to 403 ml./M.[2] with a mean of 311 ml./M.[2] If total blood volume is assumed to average between 2.5 and 3.0 L./M.[2] B.S.A.,[10,11] this represents approximately 11 per cent of the total blood volume. This value is slightly smaller than that reported by Dock and associates for their 41 patients with rheumatic heart disease (329 ml./M.[2] or approximately 12 per cent of total blood volume) and differs somewhat more from the value of 3?2 ml./M.[2] or

mately 13 per cent of total blood volume for the 29 cases of rheumatic heart disease extracted from Milnor's report.[3] The differences among these three studies, however, are all statistically insignificant ($p > 0.3$). As was the case with Dock's series, the patients with mitral disease had a larger mean pulmonary blood volume (317 ml./M.) than that of patients with aortic disease (303 ml./M.²), but this difference was not statistically significant in either study.

Reproducibility of measurements of volume. In the 5 patients in whom duplicate measurements were obtained, there was excellent agreement between the two estimates

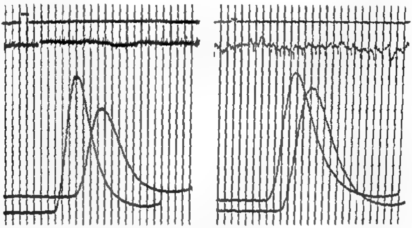

Fig. 1. Dilution curves recorded simultaneously from the left atrium and aortic root after injection of indocyanine green dye into the pulmonary artery. The curves on the left were obtained from Patient W. S. and those on the right from Patient C. S. In both cases the early curve is from the left atrium.

Table I. Summary of results

Patient	Diagnosis	B.S.A. (M.²)	HR	Arterial collection site	Cardiac output (L./min.) L.A. collection	Cardiac output (L./min.) Arterial collection	Mean cardiac index (L./min./M.²)	Mean stroke index (ml./beat/M.²)	P.A.-to-L.A. Mean transit time (sec.)	P.A.-to-L.A. Blood volume (ml./M.²)
W S	MR	2 03	90	BA	5 49	5 46	2 70	30	5 2	236
I M	MS	1 36	64		3 32		2 44	38	8 4	341
S P	MS	1 48	46	Ao	2 81	2 98	1 96	43	1? 4	405
			48	Ao	3 38	3 43	2 30	18	10 5	401
W B	MS	1 67	87		4 99		2 99	34	5 8	288
J M	AR	1 79	69	Ao	3 99	3 86	2 19	32	8 1	295
			68	Ao	4 09	3 91	? 23	33	7 5	279
F M	AR	1 6	98	BA	7 51	6 69	4 08	46	5 3	360
C S	AS	1 66	101	BA	4 30	4 79	2 59	26	5 7	245
			92	Ao	4 82	4 70	2 87	31	5 2	249
L C	AS	1 69	124	BA	6 18	6 26	3 68	30	5 2	318
M I	MS AS	1 44	98	FA	4 81	4 50	2 68	2[illegible]	7 3	376
			100	FA	4 99	4 46	2 56	26	7 5	338
G N	MS AR	2 03	68	Ao	5 16	4 3	2 43	31	7 3	97
			[illegible]	Ao	5 00	4 80	2 42	29	7 3	292

B.S.A. Body surface area. HR Heart rate. LA Left atrium. PA Pulmonary artery. BA Brachial artery. Ao Aortic root. FA Femoral artery. MR Mitral regurgitation. MS Mitral stenosis. AR Aortic regurgitation. AS Aortic stenosis.

of pulmonary blood volume. The mean discrepancy, which was statistically insignificant, was 2 ml./M.² or 0.6 per cent of the mean pulmonary blood volume of 313 ml./M.² for these 5 patients. The largest scatter around the mean of a pair of measurements was ±8 ml./M.². Measurements of cardiac output and mean transit time were also reproducible: the statistically insignificant mean discrepancy between duplicate measurements was 0.11 L./min./M.² and 0.6 second, respectively. It is of interest that pulmonary blood volume was somewhat less variable than cardiac output: the coefficient of variation for duplicate measurements was 1.5 per cent for pulmonary blood volume and 3.6 per cent for cardiac output.

Relations between pulmonary blood volume and cardiac output or stroke volume. There was a significant correlation (Fig. 3) between pulmonary blood volume and stroke volume ($r = +0.73$, $p < 0.02$). In this respect, the data are in agreement with those of Milnor and associates ($r = +0.74$, $p < 0.001$). Unlike Milnor's results, but like those of Dock and associates, the present data demonstrate no significant correlation ($r = +0.05$) between pulmonary blood volume and cardiac output (Fig. 4). It should be noted, however, that exclusion of Patient S.P., who had a bradycardia at a rate of 46 per minute, results in an appreciable improvement in correlation with cardiac output (to $r = +0.44$) along with a moderate reduction in correlation with stroke volume (to $r = +0.59$). These data, which demonstrate a relationship with cardiac output and a stronger relationship with stroke volume, correspond to the findings of Milnor and associates.

Discussion

Measurements of cardiac output from atrial dilution curves. The differences reported in the present study between cardiac outputs calculated from atrial and those from downstream dilution curves parallel the discrepancies observed by others. Dock and associates[7] in curves sampled from a peripheral artery, found that outputs calculated from pulmonary arterial injections were smaller than those from left atrial injections; the mean ratio between the two was 0.98. Milnor and associa-

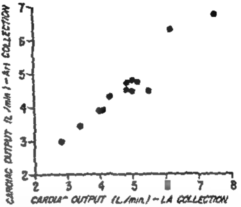

Fig. 2. The relationship between cardiac outputs measured from conventional arterial dilution curves and those measured from simultaneous left atrial dilution curves after injection into the pulmonary artery. An excellent correlation ($r = +0.98$) is evident.

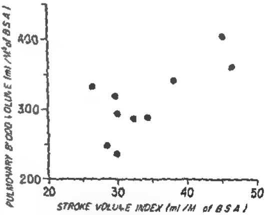

Fig. 3. The relationship between pulmonary blood volume and stroke volume.

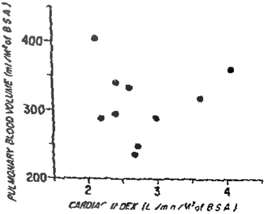

Fig. 4. The relationship between pulmonary blood volume and cardiac output.

also reported systematic differences the cardiac output calculated from left atrial injections was consistently higher than that calculated from pulmonary arterial injections by a small but significant amount (mean difference = 0 39 L per minute) They regarded the differences as unexplained It would appear however that these differences are entirely consistent with the presence of increasing magnitudes of hidden recirculation [1] under the reconstructed downslope as the injection and sampling sites are increasingly separated This phenomenon has been described previously in experiments in which with a fixed sampling site estimates of cardiac output fell as more proximal injection sites were employed [13,14] The cogency of this explanation is supported in the present data by the larger differences between atrial and peripheral arterial curves than between atrial and aortic curves If this explanation is valid the disparities cannot be ascribed to error in the atrial dilution curve but on the contrary reflect a small error in curves sampled from more peripheral sites after injection into the pulmonary artery In any event the differences as has been pointed out above are small and unimportant in the calculation of pulmonary blood volume It is concluded that pulmonary artery-to-left atrium dilution curves provide valid estimates of cardiac output

Pulmonary blood volume Previous investigators have used the Stewart Hamilton principle to calculate what has been variously termed a central intrathoracic or pulmonary blood volume According to data summarized by Dock and associates in a table adapted from Lammerant [15] average volumes calculated from peripheral arterial dilution curves in normal subjects are over 1 300 ml /M (> 60 per cent of total blood volume) with injections into peripheral veins [16, 6] and over 600 ml /M [2] (> 20 per cent of total blood volume) with injections into the pulmonary artery [17-23] Clearly these volumes because of the temporal boundaries involved do not represent pulmonary cardiopulmonary or truly central blood volume

More recently external precordial counting of isotopic indicators has been used to estimate a central circulating blood volume Isotopes have of course no intrinsic advantages over chemical indicators and precordial counting offers only the advantage of obviating the need for cardiac catheterization Using a single precordial counter to record right and left heart dilution curves Lammerant[15] and Moir and Gott[24] have obtained average values between 600 and 700 ml /M [2] both in normal subjects and in patients with mitral valve disease for a volume with temporal boundaries including half of the right heart the lungs and half of the left heart Eich and associates [8] measuring a volume with the same temporal boundaries in a series of hospitalized patients arrived at the smaller estimate of 446 ml /M [2] using a single counter and of 436 ml /M [2] using dual counters to record right and left heart curves separately Love and associates[26] attempted to measure a volume with boundaries restricted to the lung by subtracting one half of the intracardiac volumes calculated from right and left heart slopes but arrived at a mean value (490 ml /M [2]) larger than that of Eich and associates Thus precordial counting methods give results which vary among themselves presumably because of differences in detecting techniques in the time parameters employed and in the temporal boundaries involved Moreover the volumes which they measure exceed the pulmonary artery-to-left atrium volume as measured by dye dilution because of the inclusion of portions of the intracardiac volume It must be concluded that although these techniques provide convenient approximations of pulmonary blood volume potentially useful in certain investigations they measure a larger volume with indefinite boundaries

The smaller volumes reported in the present series and those reported by Milnor and associates[1] and Dock and associates and by Kuniedа [7] and Oakley and associates [25] who used Milnor s technique would appear to be the best estimates of circulating pulmonary blood volume presently available The techniques of Milnor and of Dock however suffer from certain disadvantages The need in both approaches to record and analyze two dilution curves introduces the possi

bility of cumulation of errors In addition the sacrifice of simultaneity when the two curves are obtained consecutively jeopardizes measurements during nonsteady states and the use of two indicators when the curves are obtained simultaneously introduces additional potentially troublesome technical details Moreover since two dyes cannot presently be measured by simultaneous densitometry Dock and associates used a dye and an isotope and to ensure the necessary comparability in detection techniques resorted to fractional collections of blood with the consequent introduction of a possible relatively large error in mean transit time They posited that an over all error of 20 to 30 per cent might have been introduced as a result of this and other factors

The volume calculated from pulmonary artery-to-left atrium dilution curves is expected to be an overestimate of pulmonary blood volume because of the inclusion of a portion of the blood volume of the left atrium It should be noted however that the techniques of Milnor and of Dock and their associates are also as those authors recognized subject to overestimate for the same reason With pulmonary artery-to-left atrium curves the atrial volume will be included in the calculated volume in direct proportion to the completeness of mixing in the atrial collection site With the indirect approaches of Milnor and of Dock the inclusion of the atrial volume is a direct function of the incompleteness of mixing in the left atrium as a site of injection Apparently the left atrial component is of comparable magnitude in all three approaches since the results are in substantial agreement with pulmonary blood volume ranging from 11 to 13 per cent of total blood volume

It is of interest that Blumgart and Weiss[29] in their classic studies of circulation time measured with radium C predicted on the basis of experiment plus physiologic reasoning that pulmonary blood volume which they could not directly measure would prove to be 11 per cent of total blood volume

Reproducibility of measurements In the initial studies by Milnor and associates[1] and by Dock and associates[2] duplicate measurements were not reported Recently Oakley and associates[23] have reported a standard deviation of 14 7 ml/M[2] on duplicate measurements by Milnor s technique in 12 patients and Milnor s group[30] has reported a standard deviation of 10 1 per cent on duplicate measurements in 30 anesthetized dogs From the observations of the present series it is clear that reproducibility of measurements from single atrial dilution curves is excellent This indicates both that the techniques are adequate and that the pulmonary blood volume is quite constant in patients in the usual laboratory steady state

Relations between pulmonary blood volume and cardiac output or stroke volume A relationship between cardiac output and a central blood volume which includes venous or arterial pathways or both has been reported in patients with rheumatic heart disease at rest[31] and during exercise[17] and in normal subjects at rest[1] during increases in output produced by exercise[3] and during decreases in output produced by thiopental[16] or spinal[32] anesthesia In these studies a better relation usually existed with stroke volume than with cardiac output itself[16, 1, 32] When volumes of narrower boundaries and better anatomic definition have been studied this relationship is usually but not invariably also demonstrated Thus although Lammerant[4] and Moir and Gott[4] studying mitral stenosis found that cardiac output could increase during exercise without change in the central volume measured by precordial counting Schreiner and associates[21] reported that pulmonary blood volume measured by Milnor s technique increased with exercise in patients with valvular heart disease and Levinson and associates[33] found in normal subjects and in patients with valvular heart disease that changes during exercise in lung-left heart volume (measured by dye dilution from pulmonary artery to aortic root) correlated well with a change in output and better with a change in stroke volume Moreover although Dock and associates found no correlation between pulmonary artery-to-left atrium volume and the cardiac output (and did not comment concerning stroke volume) both Milnor and associates[1] and we in the present seri found a significant relationship with st

volume. It would appear, despite differences which may be due to heterogeneity in subjects, methods, and volume boundaries, that pulmonary blood volume plays a role in the regulation of cardiac output and in particular of stroke volume.

Summary

The volume of blood in the vascular bed of the lungs can be estimated by the Stewart-Hamilton principle as the product of cardiac output and pulmonary mean transit time. Previous investigators have measured this time indirectly as the difference between transit times from the pulmonary artery and the left atrium to a peripheral artery. The present study was an investigation of the feasibility of measurement of pulmonary blood volume by the simpler and more direct approach of sampling a single dilution curve from the left atrium after injection of indicator into the pulmonary artery.

Fifteen measurements were obtained in 10 patients with valvular heart disease. In all cases the atrial dilution curves exhibited satisfactory contours and presented no difficulties in discernment of a single discrete segment of exponential decay. There was an excellent correlation (r = +0.98) between cardiac outputs measured from atrial curves and those measured from simultaneous aortic or arterial dilution curves. Pulmonary blood volumes ranged from 236 to 403 ml./M.[2] with a mean of 311 ml./M.[2], representing 11 per cent of estimated total blood volume. This value differs insignificantly from the results obtained by others who used indirect measurements of pulmonary artery-to-left atrium transit time but is appreciably smaller than earlier estimates of "central" or intrathoracic blood volume obtained from single arterial dilution curves or from isotopic techniques with precordial counting. Reproducibility was excellent, the largest scatter around the mean of a pair of measurements of pulmonary blood volume was ±8 ml./M.[2] There was a significant correlation (r = +0.73, p < 0.02) between pulmonary blood volume and stroke volume.

It is concluded (1) that dilution curves sampled from the left atrium after injection of indicator into the pulmonary artery provide valid measurements of cardiac output and permit reproducible estimates of pulmonary blood volume and (2) that the volume of blood in the vascular bed of the lungs is quite constant in the resting steady state, amounts to approximately 11 per cent of total blood volume, and may play a role in the regulation of stroke volume.

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The value of phonocardiography in the assessment of the surgical closure of ventricular septal defect

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Relatively few patients with Fallot's tetralogy or ventricular septal defect are left without any systolic murmur after surgical repair. Therefore it becomes necessary to distinguish the right ventricular ejection murmur due to residual narrowing or irregularity of the right ventricular outflow tract from the left ventricular regurgitant murmur due to residual ventricular septal defect. When the latter is present it is usually fused with the right ventricular ejection murmur.

Murmurs recorded phonocardiographically from the chest wall frequently represent a fusion of ejection and regurgitant murmurs[1] so that the usual criteria for distinguishing ejection from regurgitant murmurs[2] by the length and shape of the murmur and its relation to the first and second heart sounds cannot be applied. Amyl nitrite, which causes the ejection murmur to intensify and the regurgitant murmur to soften,[3,4] yields also a variable response or none at all when the murmurs are combined.[4] Furthermore, in the immediate postoperative period, presumably because of the heart failure present, the inhalation of amyl nitrite often fails to evoke its usual response.[4]

The frequent occurrence of complete right bundle branch block after surgery for ventricular septal defect causes a considerable delay in right ventricular events, both electrical and mechanical,[5] and we will show that this delay can be usefully employed to distinguish phonocardiographically those cases with an ejection murmur and a completely repaired septum from those with an incompletely repaired ventricular septal defect.

Material and methods

Forty five patients with Fallot's tetralogy and 36 with ventricular septal defect who had undergone open heart surgery for the repair of their defects were available for study.

Phonocardiograms were taken 3 to 4 weeks postoperatively and again 9 to 18 months later at the time of the routine postoperative cardiac catheterization study. Simultaneous tracings were recorded at the pulmonary and mitral areas and at the fourth left intercostal space, usually with

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an indirect carotid pulse recording at the mitral area to identify the mitral first sound as previously described.[8] Only tracings that were technically satisfactory could be included in this study.

In the earlier studies the New Electronic Products apparatus and photographic recorder was employed at paper speed of 75 to 80 mm. per second, and in the later ones the Elema direct writer at paper speed of 100 mm. per second.

Cardiac catheterization was performed in the usual way. The ventricular septum was assumed to be completely closed when the saturation data using rapid serial sampling with an oximeter and the dye curves recorded at a systemic artery were completely normal. When doubt existed the double venous-catheter technique was used to demonstrate and localize the shunt.

When a shunt was demonstrated, it was localized to the ventricle by saturation data or the double venous-catheter dye-curve technique in all but 2 patients in whom the shunt was assumed to be in the ventricle.

Routine postoperative electrocardiograms were studied and right bundle branch block was considered to be present when the typical disturbance of the terminal QRS vector was combined with a QRS duration of 0.11 second or more.

Results

The results are given in Table I. There were 45 patients with *Fallot's tetralogy*, 2 of whom had had second operations, making 47 postoperative assessments. Thirty-nine of these underwent early postoperative phonocardiographic studies. Complete right bundle branch block was present in 87 per cent; conduction was normal in the rest. Patients with right bundle branch block were divided into three groups. There were

Table I

Proof diagnosis	*Time of study*	*Number*	*RBBB*	*Number*	*Per cent*	*Type of murmur*	*Number*	*Proved postop. VSD*
Tetralogy of Fallot (45 cases, 47 operations)	1 mo.	39	+	34	87	Pansystolic	11	9
						Ejection	23	1
						Absent	0	0
			–	5	13	Indeterminate	5	1
						Absent	0	0
	Late	41	+	34	83	Pansystolic	8	8
						Ejection	23	0
						Absent	3	0
			–	7	17	Indeterminate	7	1
						Absent	0	0
Ventricular septal defect (3[illegible] cases, 3[illegible] operations)	1 mo.	28	+	21	75	Pansystolic	10	6
						Ejection	4	0
						Absent	7	0
			–	7	25	Indeterminate	[illegible]	1
						Absent	1	0
	Late	31	–	25	[illegible]	Pansystolic	9	7
						Ejection	6	1
						Absent	10	0
			–	[illegible]	[illegible]	Indeterminate		
						Absent		

11 with pansystolic murmurs, i.e., murmurs at the fourth left intercostal space or pulmonary area starting with or not more than 0.02 second after the peak deflection of the mitral first sound (Fig. 1). There were 23 with ejection murmurs, defined as murmurs starting at least 0.04 second or more after the first sound so that there was always a clear gap between the mitral first sound and the onset of the murmur (Fig. 2). Systolic murmurs were present in all.

In the 5 patients without right bundle branch block, ejection murmurs could not be distinguished from regurgitant murmurs on the basis of a gap between the first sound and the murmur (Fig. 3). These were simply divided into those with murmurs and those without.

Ventricular septal defects were subsequently (±1 year later) shown to be present in 9 of the 11 patients who had pansystolic murmurs and in only one of the 23 who had ejection murmurs. Of the 5 patients without right bundle branch block and loud systolic murmurs, one was shown to have a ventricular septal defect.

Forty-one phonocardiograms were satisfactory for analysis approximately 1 year after operation at the time of the postoperative catheter study. Eighty-three per cent of the patients had right bundle branch block, and the rest had normal conduction. All of the 8 patients with pansystolic murmurs were shown to have a ventricular septal defect, whereas none of the other 23 with ejection murmurs had a ventricular septal defect. Murmurs were

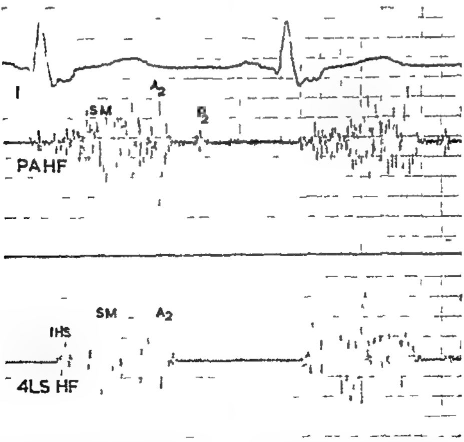

Fig. 1. Simultaneous high-frequency tracings taken at the pulmonary area and at the fourth left intercostal space in a patient with a residual ventricular septal defect after surgical repair of a Fallot's tetralogy. Paper speed is 100 mm./sec. Complete right bundle branch block is present. The first heart sound is well seen, and in the tracing recorded at the fourth left intercostal space the murmur starts 0.02 second after the first sound, indicating a left ventricular pansystolic murmur due to a residual ventricular septal defect.

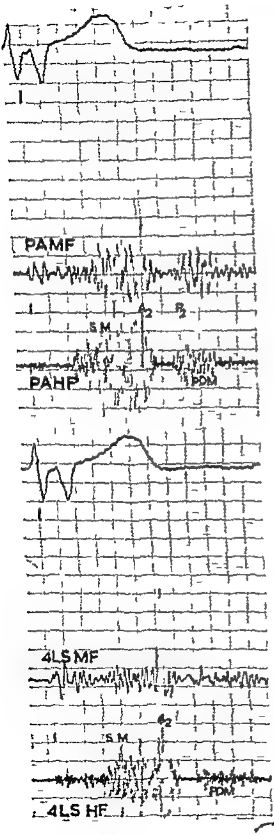

Fig 2 (For leg …)

absent in 3 and none of these had ventricular septal defects

Of the 7 patients without right bundle branch block all had systolic murmurs and one had a ventricular septal defect

In the group of 36 patients who were operated on for *ventricular septal defect* 28 phonocardiograms were available in the early postoperative phase Seventy five per cent of these patients had right bundle branch block Pansystolic murmurs were present in 10 and 6 were later shown to have ventricular septal defects Ejection murmurs were present in 4 and none had ventricular septal defects Murmurs were absent in 7 none of whom had a ventricular septal defect

Of the 7 patients without right bundle branch block 6 had systolic murmurs and one was shown to have a ventricular septal defect

Murmurs were absent in one and this patient had no ventricular septal defect

Late postoperative phonocardiograms were available in 34 patients Pansystolic murmurs were present in 9 but only 7 had ventricular septal defects Ejection murmurs were recorded in 6 and one had a ventricular septal defect Murmurs were absent in 10 and none had a ventricular septal defect

In 9 patients there was no right bundle branch block Six had systolic murmurs and one of these had a ventricular septal defect Murmurs were absent in 3 none of whom had a ventricular septal defect

Discussion

Saturation data alone are notoriously unreliable in detecting small postoperative ventricular septal defects Systemic dye curves are a little better and a normal dye curve probably excludes a shunt of more than 10 to 15 per cent Sampling techniques

Fig 2 High frequency and medium frequency tracings recorded consecutively at the pulmonary area and fourth left intercostal space in a patient with Fallot s tetralogy 1 year postoperatively Complete right bundle branch block is present and the murmur at both areas clearly starts 0 12 second after the first sound This is a right ventricular ejection murmur and indicates a closed ventricular septum In this case there is also a murm… monary insufficiency which occurs after … pulmonary component of the sec…

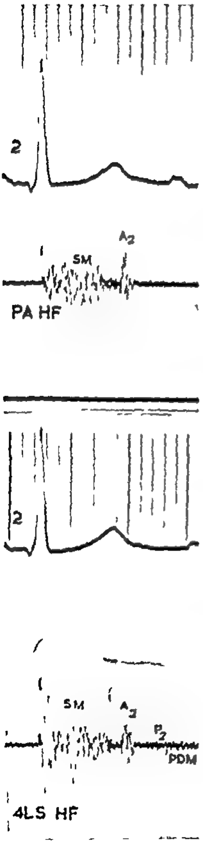

Fig. 3 (For legend see opposite column.)

using two venous catheters were employed in a minority of patients so that in most of our postoperative studies we can only claim to have excluded ventricular septal defects with left to right shunts of more than 10 per cent. From the practical viewpoint, shunts of smaller magnitude are not of any consequence.

The studies of Goldblatt and associates[3] have shown that with few exceptions surgically induced right bundle branch block causes a delay in the onset of right ventricular contraction. Since the murmur of ventricular septal defect starts with or soon after left ventricular contraction, whereas ejection murmurs produced by irregularities or mild obstruction of the right ventricular outflow tract occur shortly after the onset of right ventricular ejection, the time of onset of the two types of murmur should be significantly different when right bundle branch block is present (Fig. 4).

In the patients with Fallot's tetralogy the demonstration of a pansystolic murmur some months after operation invariably indicated the existence of a ventricular septal defect. However, the diagnostic accuracy of a pansystolic murmur in the early postoperative phase was less—only 9 out of 11 patients with such murmurs had a ventricular septal defect. Similarly, in the early studies on postoperative ventricular septal defects only 6 out of 10 patients with pansystolic murmurs were shown to have ventricular septal defects, whereas at the time of the later study 7 of 9 had ventricular septal defects.

There are several possibilities. Firstly, all pansystolic murmurs recordable at the fourth left intercostal space are not necessarily due to ventricular septal defect. Some may be due to mitral insufficiency as was shown in one patient with a ventricular septal defect and corrected transposition. Secondly, it is quite possible that a pansystolic murmur in the early post

Fig. 3. Consecutive high frequency tracings at the pulmonary area and fourth left intercostal space in a patient after repair of a ventricular septal defect (paper speed 80 mm./sec.). Here there is no bundle branch block, so that the murmur in this case starts soon after the first sound, making it impossible to distinguish right ventricular ejection murmurs from left ventricular regurgitant murmurs.

operative phase may in fact be due to a ventricular septal defect and that its subsequent disappearance 1 year later (as occurred in 2 of our patients) could be due to spontaneous closure of the small residual defect Thirdly it is possible that in some cases the electrocardiographic pattern of right bundle branch block may not be associated with the delay in right ventricular mechanical events as Goldblatt and associates[8] have shown Ejection murmurs might then be easily misinterpreted as pansystolic murmurs due to a residual ventricular septal defect Unfortunately our own routine recordings of right ventricular pressures before and after operation are recorded at paper speeds of 80 mm per second which do not allow sufficiently accurate measurements of the delay in the onset of right ventricular contraction to be made

Lastly it must be accepted that our routine postoperative catheter methods might be insufficiently sensitive to detect some small ventricular septal defects

Tricuspid insufficiency is a not infrequent finding at the time of operation and in the early postoperative period but theoretically in the presence of right bundle branch block the onset of the murmur should be delayed starting with the tricuspid component of the first heart sound This has been confirmed in one patient (not included in this series) with a closed ventricular septal defect and organic tricuspid incompetence a sequel of bacterial endocarditis

Of the 27 patients from both groups who had ejection systolic murmurs in the early postoperative phase only one was subsequently found to have a ventricular septal defect However the murmur in this

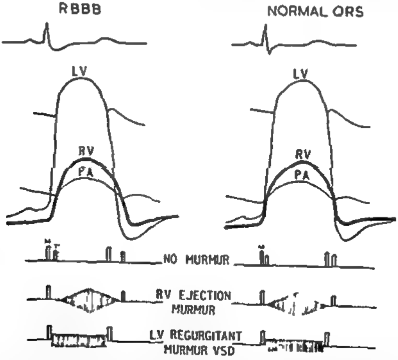

Fig 4 Schematic representation of right and left ventricular mechanical events in the presence of right bundle branch block and with normal conduction In the former right ventricular ejection is delayed so that ejection murmurs start well after the mitral first sound leaving a clear gap between the second sound and the onset of the murmur When ventricular septal defect is present the murmur starts soon after the mitral first sound leaving no appreciable gap When normal conduction is present right and left ventricular events are insufficiently separated to cause a clear difference in the time of onset of right ventricular ejection and left ventricular regurgitant murmur

subject became pansystolic by the time of recatheterization, which suggested that a leak had developed subsequent to the early postoperative phase.

Of 29 patients with ejection murmurs in the late postoperative study, only one was shown to have a small residual ventricular septal defect. There is no clear explanation for this exception.

When right bundle branch block is absent, differentiation between ejection and pansystolic murmurs by this method is not possible. It is not surprising, therefore, to find that 2 out of 11 patients in the early postoperative group and 2 of 13 in the late postoperative group had ventricular septal defects.

Systolic murmurs not infrequently disappeared with the passage of time. All patients with Fallot's tetralogy had murmurs of some sort in the early postoperative phase, but 3 lost their murmurs by the time of the late postoperative study. Eight patients with ventricular septal defects had no murmurs in the early postoperative period, whereas 13 had no murmurs when the study was repeated some months later. All 16 patients without murmurs were shown to have an intact ventricular septum. The disappearance of murmurs as time passes is presumably due to involution of residual hypertrophy of the outflow tract, the gradual smoothing out of irregularities produced by sutures and patches, and the disappearance of tricuspid incompetence.

Summary and conclusions

Forty-nine patients with Fallot's tetralogy and 36 with ventricular septal defect were studied approximately 1 month and again 1 year after surgical closure of their defects.

The study of high-quality phonocardiograms 1 year after operation enabled us to distinguish patients with left ventricular regurgitant murmurs from those with right ventricular ejection murmurs only when surgically induced right bundle branch block was present. When the former type of murmur was present, all but 2 of 17 patients were shown to have residual ventricular septal defects, and when the latter type of murmur was present, only one of 29 had a residual ventricular septal defect.

In the absence of right bundle branch block, ejection and regurgitant murmurs could not be clearly distinguished phonocardiographically.

In relatively few cases were no murmurs present, and in all the ventricular septum was shown to be closed.

The immediate postoperative tracings were less satisfactory, and the possible reasons for this and for the exceptions previously noted are discussed.

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The electrocardiogram in the first two days of life. An interracial study

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It is well recognized that from time to time T wave changes are encountered in the electrocardiogram which have no known pathologic significance. In the absence of certain physiologic stimuli[1-7] these nonspecific deviations from the normal are very uncommon in the electrocardiograms of healthy White adults. In contrast, however, isolated precordial T wave changes are frequently found in the electrocardiograms obtained from Negro subjects.[1,8-11] In the Bantu of South Africa similar changes have been noted and the electrocardiogram is regarded as being unstable.[12,13] In a previous study reported from Cape Town[14] these changes have been noted in the local Bantu but not in the White or in the Cape Coloured.

Whether the differences in the electrocardiographic pattern is due to environmental or inherent genetic factors has not been determined. Therefore an interracial electrocardiographic study of White, Coloured, and Bantu subjects in various age groups was considered to be worth while. Furthermore, current interest in cardiorespiratory problems in newborn infants made it essential to establish normal criteria for each racial group in our multiracial society. This report concerns our findings in the first 48 hours of life, taking into consideration the wide variations in health and the rapid day-to-day changes that occur in this age group.[1]

Material and methods

All tracings were recorded by the authors after a full clinical examination had revealed nothing suggestive of cardiovascular abnormality. The infants were all in good general condition and unselected. The standard limb, unipolar, and precordial leads V_1 to V_6 were taken routinely. The Sanborn Viso-Cardiette direct writing electrocardiograph correctly standardized was used for all records.

Almost all the White infants were from the Mowbray Maternity Hospital and the Coloured and Bantu from either the Salvation Army Maternity Hospital or the New Somerset Hospital. These are all institutions in Cape Town which employ similar techniques for delivery and which are staffed by members of the University of Cape Town obstetrical service.

There were 30 infants under 24 hours of age and 30 between 24 and 48 hours in each racial group, i.e., 180 infants in all.

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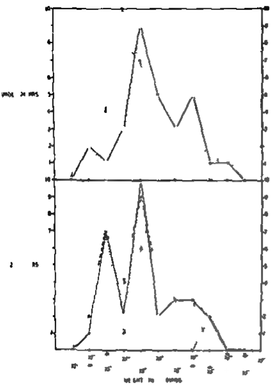

Fig. 1. The distribution of the three racial groups by weight at birth is shown. Solid black line = Whites. Dashed line = Coloured. Dotted line = Bantu.

The distribution by weight is shown in Fig. 1. The average birth weights in the first 24 hour period were 7 pounds and 9 ounces in the Whites, 6 pounds and 13 ounces in the Coloured, and 7 pounds and 7 ounces in the Bantu. In the second 24 hour period the average weights were 7 pounds and 3 ounces, 6 pounds and 11 ounces, and 7 pounds and 5 ounces, respectively. The heaviest infants were in the Bantu group; 3 weighed between 10½ and 11 pounds. No infant weighed 5½ pounds or less.

Unfortunately, the sex was not recorded in every instance. There were 26 male and 34 female White infants, at least 27 male and 23 female Coloured infants, and at least 22 male and 28 female Bantu infants.

Results

Heart rate and rhythm. The mean heart rate in the first 24 hours was 133 beats per minute in the White group, 125 beats per minute in the Coloured, and 126 beats per minute in the Bantu. Between 24 and 48 hours of age the figures were 151, 140, and 147 beats per minute, respectively. Sinus rhythm was present in every instance.

The mean P wave amplitudes in Leads II, V_1, and V_6 are shown in Table I. There was no difference in mean P wave duration in the three groups (0.05 second) at both age periods (range 0.03 to 0.08).

Notching of the P wave in the precordial leads other than in Leads V_5 and V_6 was a fairly common finding (30 per cent), with notching of P_2 in 12 per cent.

P-R interval and duration of QRS. The mean P-R interval in Lead II is shown in Table II, and the mean QRS in Table III. The maximum and minimum values are shown in parentheses.

QRS and T wave axes in frontal plane. The mean QRS and T wave axes in the frontal plane are shown in Table IV. During the first 24 hours the QRS axis in the Bantu is to the left of that in the White. In all groups the T wave axis shifts markedly to the left in the second 24 hours.

Q waves in precordial leads. There were 3 White, 5 Coloured, and 5 Bantu infants under the age of 24 hours with Q waves in Lead V_6. Between 24 and 48 hours of age figures were also 3, 5, and 5, respectively. Therefore, Q waves in Lead V_6 were found in 10 per cent of White infants, 17 per cent of Coloured, and 17 per cent of Bantu.

A Q_{V1} was encountered only once (in a White infant within the first 2 hours of life).

Mean voltage of R and S in Leads V_1 and V_6. The mean voltages of R and S in Leads V_1 and V_6 and the R/R+S percentage is shown in Table V. R approximates S in the Bantu, whereas R and S are widely divergent in the other two groups, especially during the first 24 hours.

Distribution of R and S patterns in Leads V_1 and V_6. The distribution of R and S patterns in Leads V_1 and V_6 is shown in Table VI.

Because individual precordial patterns are not reflected in Table VI, the classification of Furman and Halloran[20] has been adopted (Table VII). (1) The normal pattern: Here R waves in Leads V_1 and V_6 are greater than S. T is usually inverted in V_1, and an upright T or a Q

wave is usually present in V_6. (2) 'Deep S in V_1' pattern. This is similar to the first except that S in Lead V_1 is equal to or greater than the accompanying R wave. (3) 'Deep S in V_6' pattern. This is similar to the first except that S in Lead V_6 is equal to or greater than the accompanying R wave. (4) S waves across entire precordium are equal to or greater than the R waves. The difference between individual patterns in White, Coloured, and Bantu infants is shown in Table VII.

Extent of T wave inversion in precordial leads. The extent of T wave inversion in the precordial leads is shown in Table VIII. Where T waves were diphasic they were considered to be inverted if the initial phase was negative. Apart from the total which indicates the number of electrocardiograms which showed T wave inversion in a particular lead, the figure at the bottom of each column in Table VIII indicates the number of subjects in whom T wave inversion was first detected in

Table I. Mean P wave amplitude in Leads II, V_1, and V_6

Age	*Lead*	*White*	*Coloured*	*Bantu*
Under 24 hr	II	1.3 mm (1.0-2.5)	1.2 mm (0.5 to 3)	1.0 mm (−1 to 2)
	V_1	1.0 mm (−1 to +3)	1.0 mm (0 to 2)	1.2 mm (−0.25 to 3.5)
	V_6	1.0 mm (1 to 1.5)	1.0 mm (0.5 to 2)	1.0 mm (0.5 to 2)
24-48 hr	II	1.2 mm (1 to 2.5)	1.4 mm (0.5 to 3.5)	1.1 mm (0.5 to 2)
	V_1	1.0 mm (−1 to 2)	1.2 mm (0.5 to 3)	1.1 mm (−0.5 to 2.5)
	V_6	1.3 mm (0.5 to 2)	1.1 mm (0.5 to 2)	1.0 mm (0.5 to 2)

Table II. Mean P-R interval (sec.) in Lead II

Age	*White*	*Coloured*	*Bantu*
Under 24 hr	0.09 (0.08-0.14)	0.10 (0.08-0.12)	0.10 (0.07-0.13)
24-48 hr	0.10 (0.08-0.12)	0.10 (0.08-0.13)	0.11 (0.08-0.12)

Table III. Mean duration of QRS (sec.) in Lead II

Age	*White*	*Coloured*	*Bantu*
Under 24 hr	0.05 (0.03-0.08)	0.04 (0.04-0.06)	0.05 (0.03-0.06)
24-48 hr	0.04 (0.03-0.06)	0.04 (0.04-0.06)	0.04 (0.03-0.07)

Table IV. QRS and T wave axes in the frontal plane

Age	*White*		*Coloured*		*Bantu*	
	QRS	*T*	*QRS*	*T*	*QRS*	*T*
Under 24 hr	+150 (+110 to +180)	+75 (−40 to +150)	+137° (+80 to +180)	+90 (−30 to +180)	+133 (+90 to +210)	+80 (−70 to +170)
24-48 hr	+140 (+100 to +180)	+25 (−60 to +60)	+140° (+50 to +210)	+50 (−10 to +140)	+137 (+85 to +180)	+45 (−60 to +130)

Table V. Mean voltage of R and S in Leads V_1 and V_6 and the R/R+S percentage

Age	White		Coloured		Bantu	
	V_1R	V_1S	V_1R	V_1S	V_1R	V_1S
24 hr	12.5 (6-28) 63%	7.5 (0-34)	13.5 (6-27) 67%	6.7 (0-30)	12.5 (3-26) 53%	11.1 ([illegible]-32)
24-48 hr	11.2 (1-31) 67%	5.5 (0-21)	14.1 (7-24) 66%	7.4 (0-20)	12.5 (2-21) 58%	9.1 (0-20)
	V_6R	V_6S	V_6R	V_6S	V_6R	V_6S
24 hr	7.5 (2-10) 40%	11.2 (4-22)	6.9 (1-20) 40%	8.5 (0-15)	7.8 (1-19) 49%	8 (0-15)
24-48 hr	5.2 (0.5-13) 35%	9.6 (1-28)	8.6 (2-22) 47%	9.5 (2-15)	8 (1-16) 53%	7.1 (0-23)

Table VI. Distribution of R and S patterns in Leads V_1 and V_6

Age	Pattern	Lead V_1			Lead V_6		
		White (%)	Coloured (%)	Bantu (%)	White (%)	Coloured (%)	Bantu (%)
Under 24 hr	R	10	3.3	0	0	3.3	3.3
	R > S	69.9	73.2	56.6	20	36.6	50
	R = S	6.7	6.7	3.3	0	0	0
	R < S	13.3	16.7	40	80	60.0	46.6
24-48 hr	R	3.3	3.3	3.3	0	0	6.7
	R > S	73.3	83.2	66.6	13.3	36.6	33.3
	R = S	3.3	3.3	3.3	3.3	3.3	13.3
	R < S	20	10	26.6	83.[illegible]	60.0	46.6

that lead. The horizontal columns from V_1 to V_6 indicate the number of subjects in whom T wave inversion persisted from the initial number on the left through individual leads to V_6.

Thus, for example, it can be seen that no White infant under 24 hours of age showed T wave inversion from Lead V_1 through Lead V_6. T wave inversion in Lead V_6 was found in 7 White, 13 Coloured, and 10 Bantu infants within the first 24 hours of life and in 6 White, 6 Coloured, and 8 Bantu infants in the 24-48 hour period. Thus a total of 50 instances of T wave inversion in Lead V_6 was encountered, i.e., an over-all incidence of 28 per cent.

A further point of interest is the increased number of subjects who showed T wave inversion in Lead V_1 in the second 24 hour period as compared with the first period. In the first 24 hours a total of 20 infants, i.e., 22 per cent, showed T wave inversion in Lead V_1, and the corresponding figures for the second 24 hour period was 48 per cent.

Discussion

There have been many studies on the electrocardiogram in infancy.[17-34] However, only those reports which deal with the immediate neonatal period will be discussed, and premature infants have been excluded. We know of no other study in which an interracial comparison has been made; in fact, few reports mention the race of the infants concerned. Kessel[1] reported on 15 Bantu infants, Cruge and Harned[29] reported on 61 White and Negro infants, and Rothfeld and associates[17] reported on 50 infants, 39 of whom were Negro.[27]

Our findings for heart rate are in keeping with those of other studies.[3, 6, 9, 21]

We have not encountered the arrhythmias noted by others[17] On two occasions the P wave amplitude in Lead II exceeded 2 5 mm and there was a tendency for the amplitude to be higher in White than in Bantu infants In common with Furman and Halloran[9] the maximum P wave duration noted was 0 08 second The P R interval in our series varied over a slightly wider range than that previously reported[9] Our mean QRS duration was consistent with other series[17,20] and we report a single finding of 0 08 second In the first 24 hours of life we found the mean QRS axis to be more to the right in the White group than in the Bantu group The striking shift of the T wave axis to the left in all groups in the second 24 hours is in keeping with the findings in other series

The presence of Q waves in the left precordial leads notably in Lead V_6 has been confirmed by most authors with a maximum reported incidence of 73 5 per cent[21] Our highest incidence (17 per cent) was in the Coloured and the Bantu In common with Rothfeld and associates[17] we report a single instance of a Q wave in Lead V_1

The fairly consistent finding of a dominant R wave in the right chest leads has been well documented and was present in our series All groups showed this feature in a majority of electrocardio

Table VII *Relationship of R and S waves in the precordial leads as classified by Furman and Halloran*[9] *in all 180 patients*

Group	*Deep S across praecordium*	*Deep* S_{V6}	*Deep* S_{V1}	*Dominant R in V and V normal*
White	17	66	5	12
Coloured	15	45	10	30
Bantu	26	26	14	34

Table VIII *T wave inversion*

Age	*Lead I*			*Lead I*			*Lead* V_1			*Lead I*			*Lead* V_4			*Lead I*		
	W	C	B	W	C	B	W	C	B	W	C	B	W	C	B	W	C	B
Under 24 hr	7	11	2	6 5	10 1	2 0	4 5 2	8 1 1	2 0 5	2 5 2 2	6 1 1 2	2 0 4 5	0 4 2 1 0	5 1 1 [illegible] [illegible]	2 0 4 4 0	0 2 2 1 0 [illegible]	5 1 1 2 2 2	2 0 3 4 0 1
Total	7	11	[illegible]	11	11	2	11	10	7	11	10	11	7	11	10	7	13	10
24-48 hr	15	13	15	11 1	11 5	10 0	9 0 [illegible]	9 3 0	9 0 5	4 0 2 [illegible]	5 2 0 1	5 0 [illegible] 1	3 0 2 [illegible] 1	3 1 0 1 2	4 0 2 1 0	3 0 2 1 0 0	[illegible] 1 0 1 1 1	4 0 [illegible] 1 0 1
Total	15	13	15	1[illegible]	16	10	11	[illegible]	14	8	8	8	8	7	7	6	[illegible]	8

W White C Coloured B Bantu

Fig. 2. Examples of precordial lead patterns. *A*, Deep S_{V4}. Most frequent pattern in the White and Coloured groups. *B*, Normal. (Dominant R in Leads V_1 and V_4.) Most frequent pattern in the Bantu. *C*, Deep S_{V1}. Highest incidence in the Bantu. *D*, Deep S across the precordium. Highest incidence in the Bantu. Note the T wave inversion in Lead V_1.

grams, but it was particularly striking in the White group. In Lead V_4 the picture was more variable. The great majority of White infants and also the bulk of the Coloured infants showed a dominant S wave in this lead. However, the Bantu demonstrated a tendency toward either a dominant R or biphasic (R/S) complex in this lead. Table VI shows the differences in percentage distribution of patterns in Leads V_1 and V_4 and these differences have been shown to be statistically significant in Lead V_1 in the first 24 hour period ($p = < 0.02$) and in Lead V_4 in both age periods ($p = < 0.01$). Our mean values for R and S in these two leads are

shown in Table V and Table VII shows the distribution of our tracings according to the pattern across the entire precordium not in Leads V_1 and V_6 only Deep S in V_6 gives a good indication of the complete reversal of R/S progression of Alimurung and associates[18] and deep S in V_1 of the adult electrocardiogram[17] Once again the racial difference between White and Bantu is apparent with the former pattern more common in the White and the latter more common in the Bantu Examples of the patterns discussed are shown in Fig 2 It is probable that the frequency of the adult pattern found by Rothfeld and associates[17] is due to the predominantly Negro distribution of their material Furthermore we also found that the R/S ratio in Lead V_6 differed somewhat between the Bantu male and female A difference between the adult Bantu male and female has been shown by *Brink*[13]

Because of the variability[20 21 8] doubt has been cast on the value of QRS complexes for interpretive purposes in the first weeks of life However Scott and Franklin[22] claim that the Q R and S waves are stable during this period We believe that the differences which we have shown in the precordial leads signify the greater emergence of the left ventricle in the Bantu than in the White during the first 48 hours of life This is supported by the higher incidence of Q waves in Lead V_6 and by the lesser degree of right axis deviation in the Bantu group

The independent nature of the T wave relative to the QRS has received repeated mention[18 20 30] In Lead V_1 the T wave is usually upright on the first day of life[18 25] and then progressive inversion follows[18] In Lead V_6 the T wave is usually upright in the first 5 minutes after birth then becomes negative over the next 24 hours[21] and later is upright again[25] T wave inversion in Lead V_6 was not uncommon in early infancy in some series[3 4 20] but this has not been the experience of others[19 5]

We have not tabulated the incidence of positive T waves in our series but with very few exceptions this wave was clearly upright when not inverted and accordingly the incidence can be inferred from Table VIII Thus upright T waves in Lead V_1 were found with greater frequency in the first 24 hour period than in the second in all three racial groups and was particularly striking in the Bantu

We have not discussed the possible reasons for the racial differences encountered but these include genetic considerations the physiologic adjustment to post natal life anatomic considerations such as closure of the foramen ovale and ductus arteriosus and in the Bantu the possibility of postmaturity[36]

Summary

1 Electrocardiograms of 30 normal healthy full term White infants under 24 hours of age and of 30 between 24 and 48 hours of age were studied and compared with the electrocardiograms of equal numbers of Coloured and Bantu infants in the same time periods—180 infants in all

2 No significant differences between the three racial groups were noted in heart rate rhythm P wave duration and T wave axes

3 The P wave amplitude in Lead II tended to be higher in the Whites than in the Bantu The QRS axis tended to be more to the right in the Whites than in the Bantu

4 Q waves in Lead V_6 were found more often in the Bantu and Coloured infants than in the White

5 The most striking difference between the White and Bantu neonatal electrocardiograms was found in the QRS complexes in the precordial leads In Lead V_1 during the first 24 hours more White than Bantu infants showed right ventricular dominance In Lead V_6 during both age periods more Bantu than White infants showed left ventricular patterns The differences were statistically significant The electrocardiograms of the Coloured fell between these two troups

6 T wave inversion in Lead V_6 was found more commonly in the Bantu and Coloured than in the White

7 The literature on the electrocardiographic pattern of normal healthy infants during the first few days of life is reviewed and our findings are compared with the reported normal standards

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Late systolic murmur of mitral regurgitation

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The late systolic murmur has its onset in mid systole and occupies all of late systole where it crescendos to the second heart sound. The murmur has been encountered without evidence of organic heart disease and has been considered to be an innocent finding.[1,2] More commonly it appears in association with a specific lesion such as (a) left ventricular outflow obstruction (subaortic stenosis[4-7]), (b) coarctation of the aorta,[8] (c) the Marfan syndrome,[9] (d) after a myocardial infarction[10] or pericarditis,[11] and (e) mitral regurgitation.[11-13]

This discussion considers the auscultatory and pathophysiologic aspects of the late systolic murmur in the patient with mitral regurgitation. It is based on a correlation of external and intracardiac phonocardiographic studies with catheterization and angiocardiographic data. The specific purposes are to (a) establish the late systolic murmur as a useful sign of mitral regurgitation, (b) define the auscultatory features of the murmur in terms of its graphic registration, (c) differentiate the murmur itself and its implications from the type of pansystolic murmur with vibrations in early systole and major sound elements in late systole, (d) describe the angiocardiographic findings associated with the late systolic murmur, and finally (e) identify what appears to be the extent of the physiologic abnormalities which accompany this murmur.

Material

Eight patients who ranged in age from 21 to 59 years were studied. Four were male. No history of rheumatic activity or its stigmata was offered by any of these individuals. In each instance the murmur was reported as having been first noted during adult life without a discernible relation to any specific illness.

The patients essentially were well. Very mild effort dyspnea was recorded by 2 and the sensation of rapid or irregular heart action again after effort was indicated by 6 individuals. However, the presence of the murmur, originally discovered during a routine physical examination, was the major issue which involved these patients in a subsequent investigation.

Methods of study

Each of the patients was submitted to a routine physical evaluation including an electrocardiogram and a comprehensive

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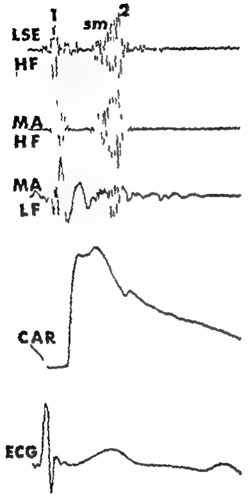

Fig. 1. The late systolic murmur (*SM*) is shown on the high frequency (*HF*) phonocardiograms in the mitral area (*MA*) and fourth left intercostal space along the left sternal edge (*LSE*). The murmur begins in mid systole after the first heart sound (*1*) and increases in intensity to the aortic component of the second heart sound (*2*). The high frequency murmur is not seen on the low frequency (*LF*) phonocardiogram. An indirect carotid pulse (*CAR*) and electrocardiogram (*ECG*) are taken simultaneously for precise timing of the first (*1*) and second heart sound (*2*).

roentgenologic analysis of the size of the heart.

The external phonocardiogram was obtained with a 5-channel direct writing Schwarzer apparatus.

The intracardiac sounds were recorded with the Allard Laurens micromanometer simultaneously with the cardiac pressures during catheterization of the right and left sides of the heart. Left ventriculography and aortography were performed in each of the patients and recordings were made cineradiographically.

Results

In each patient the late systolic murmur was heard best at the apex of the heart where the intensity varied from Grade 2 to 4 (grading of 1 to 6). Transmission along the left sternal border to the pulmonary and aortic valve areas was observed in 3 patients. In each instance the murmur appeared to start in mid systole and the intensity increased in crescendo fashion terminating with the second heart sound. The first heart sound was normal and the degree of splitting of the second heart sound was normal during both phases of respiration.

External phonocardiography confirmed all the essential details observed on clinical auscultation (Fig. 1). Initial vibrations were not seen in early systole. They started in mid systole, increased during late systole, and ended with closure of the aortic valve. The murmur enveloped the second heart sound in 2 patients, extending into the period of isometric relaxation. Splitting of the second heart sound varied from single to 0.03 second on expiration and from 0.02 to 0.06 second on inspiration. Third heart sounds were not recorded.

Intracardiac phonocardiography showed that the murmur developed in the left ventricle below the mitral valve in the path of the regurgitant jet which was demonstrated angiocardiographically. The murmur disappeared whenever the catheter was placed at the apex or outflow tract of the left ventricle (Fig. 2). A third heart sound was recorded uniformly, but this was not transmitted to the chest wall.

The electrocardiogram was normal in 6 patients. In 2 the total voltage of the S wave in Lead V_1 and the R wave in Lead V_5 exceeded 37 mm. However, RST segment deviations suggestive of left ventricular hypertrophy were not seen in these tracings.

On roentgenographic examination, the heart size was judged to be within normal limits in all but 2 of the patients who were believed to have the minimum indications of left ventricular enlargement. These were not the same individuals who had increased electrocardiographic voltages.

The catheterization studies showed that the cardiac outputs were normal from 4 6 to 5 1 liters per minute Pulmonary arterial and left atrial pressures and pulse contour were normal averaging 20/6 and 8 mm Hg respectively Pressure gradients were not demonstrated across the mitral or aortic valves

The cineradiographic views of left ventriculography uniformly indicated bulging of the septal leaflet of the mitral valve during early systole (Fig 3) This was succeeded by a Grade II reflux (Grading I to IV) of the radiopaque material into the left atrium during late systole (Fig 4)

Aortography failed to indicate any structural or functional abnormality of the aortic valves or any evidence of obstruction of the left ventricular outflow tract in any of the patients

Discussion

This investigation establishes the presence of a late systolic murmur in association with mitral regurgitation The historical facts offered by the patients studied indicate no etiology for the mitral valve incompetence At least from the evidence available it appears that the mitral regurgitation developed independently of rheumatic fever or in association with an attack so subtle that it was not recognized clinically Any indication that the functional incompetence of the valve resulted from a congenital structural defect is mitigated by the fact that the murmur was not discernible either at birth or during early childhood However one may still argue that the structural weakness did exist at birth but was of such modest proportion that it matured only with the passage of time

The graphic registration of the late systolic murmur which were obtained externally and from within the heart itself established that it has its onset in mid systole and increases in intensity until it terminates with the second sound Furthermore it may actually envelop this sound That the murmur is produced at the inflow tract of the left ventricle just below the mitral valve leaflets has also been ascertained

The left ventriculography studies suggest that the regurgitant flow of blood across the mitral valve is of modest proportion Antecedent to this event the septal leaflet of the mitral valve is seen to bulge in response to the early pressures exerted by ventricular contraction However it does not permit the retrograde passage of blood into the left atrium until the latter phase of systole

The moderate degree of regurgitation and the relatively limited pathophysiologic consequences are confirmed not only by the normalcy of the electrocardiogram and heart size but also by the normal

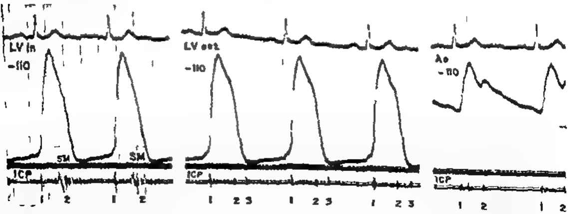

Fig 2 Intracardiac phonocardiography (*ICP*) demonstrates the late systolic murmur (*SM*) extending into the period of isometric relaxation in the inflow *tract of the left* ventricle (*LV in*) This murmur disappears when the phonocatheter is positioned at the apex and outflow *tract of the left* ventricle (*LV out*) There is an early systolic murmur in the aorta (*Ao*) beginning after the first heart *sound* (*1*) and ending before the second heart sound (*2*) this murmur is frequently seen in normal subjects A third heart sound (*3*) is present in the left ventricle (*LV*) 0 14 second after the aortic component of the second heart sound (*2*)

cardiac outputs and left atrial and pulmonary arterial pressures which were revealed by cardiac catheterization.

In most instances, patients with mitral regurgitation are observed to have a pansystolic murmur which begins with the first heart sound and continues to closure of the aortic valve, sometimes extending into the period of isometric relaxation.[14,15] Since in mitral regurgitation the left ventricular pressure exceeds the left atrial pressure from isometric contraction to isometric relaxation, there is an acceptable physiologic explanation for the timing and configuration of this murmur.

Fig. *3.* Left ventriculogram recorded by cineradiography in the right anterior oblique position demonstrates bulging of the septal leaflet of the mitral valve during early systole. The injection of radiopaque material is made through the catheter positioned at the apex of the left ventricle (*LV*).

Fig. *4.* During late systole the large left atrium (*LA*) in the right anterior oblique position fills with radiopaque material. Mitral regurgitation (*C* and *II*) is confined to late systole.

A small number of patients with mitral regurgitation may show, at least on phonocardiographic registration, a murmur with small, almost inconsequential, vibrations in early systole but with major vibrations in late systole which increase in intensity until they terminate at the second heart sound.[16] The late systolic murmur demonstrated in the patients included in this investigation must be differentiated from this latter type of pansystolic murmur. It is pertinent to emphasize that the late systolic murmur under discussion does not demonstrate, on graphic registration, vibrations in early systole. It may be that

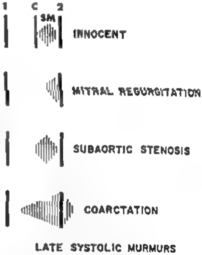

Fig. *5.* Late systolic murmurs (*SM*) are often innocent. The murmur is frequently initiated by a loud systolic click (*C*). This late murmur often is diamond shaped and ends before the second heart sound (*2*). In patients with mitral regurgitation the late murmur crescendos to the second sound. The late diamond-shaped murmur also originates from the hypertrophied outflow tract of the left ventricle in patients with subaortic stenosis. The late murmur in patients with coarctation of the aorta is often longer, beginning after the first heart sound (*1*) and increasing in intensity to envelop the second sound with a short diastolic component.

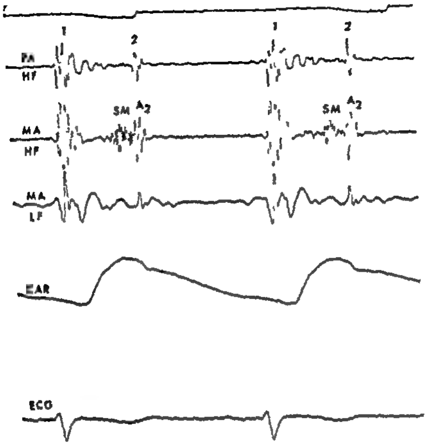

Fig 6 High frequency phonocardiogram (*HF*) from the pulmonary area (*PA*) and mitral area (*MA*) are taken in a patient with subaortic stenosis Low frequency phonocardiogram (*LF*) from the mitral area (*MA*) is also shown with a simultaneous indirect carotid pulse (*CAR*) and electrocardiogram (*ECG*) The apical late diamond shaped systolic murmur (*SM*) begins in mid systole after the first heart sound (*1*) and ends before the aortic component (A_2) of the second heart sound (*2*) which is almost synchronous with the dicrotic notch of the indirect carotid pulse

the genesis of the structural defect the deformity itself and the functional abnormality of the mitral valve differ considerably in both instances

The late systolic murmur due to mitral regurgitation must be differentiated from that which is associated with other causes (Fig 5)

The *innocent late systolic murmur* often called a cardiorespiratory murmur is frequently initiated by a loud systolic click that is best heard at the apex[1,2] This murmur is generally Grade 1 to Grade 3 in intensity beginning in mid systole and is diamond shaped ending before closure of the aortic valve Changes in posture and respiratory variation produce striking alterations in its frequency and intensity These murmurs may be produced by compression of a lung segment by the left ventricle or they may originate from vibrations of pericardial thickening pleural or pericardial adhesions They may disappear as the patient becomes older The first and second heart sounds are normal Palpation reveals no evidence of right or left ventricular hypertrophy The carotid and jugular venous pulsations are normal

Patients with *subaortic stenosis* may demonstrate a late systolic murmur which originates from the hypertrophied a

Fig. 7. Left ventriculogram in the right anterior oblique position demonstrates an abnormal indentation in the mid-diaphragmatic portion of the left ventricle (*LV*) suggestive of a localized hypertrophy or band.

tract of the left ventricle.[4,7] During ventricular systole there is functional contraction of the outflow tract which creates turbulence in mid systole and late systole. This murmur is best recognized along the left sternal border and sometimes at the apex, and is associated with other prominent findings of subaortic stenosis. In our experience with 3 patients who had hypertrophy of the outflow tract of the left ventricle, the external and intracardiac phonocardiograms showed the murmur to be diamond shaped and confined to late systole (Fig. 6). The murmur was demonstrated in the outflow tract of the left ventricle and in the aorta above the aortic valve. Left ventriculography showed subaortic narrowing during late systole in 2 patients, and in one a functional obstruction below the level of the mitral valve with a chamber formation beginning in mid systole (Fig. 7).

Coarctation of the aorta may be associated with a late systolic murmur.[8] This murmur, generated by flow through the aortic narrowing or through dilated collateral vessels, is delayed to late systole because of its origin at a distance from the heart. Such murmurs are usually of maximal intensity in the left upper chest and are often followed by a diastolic component. The carotid pulse shows a rapid upstroke due to the increased pulse pressure, and the femoral pulse is delayed when compared to the carotid pulse. The left ventricle also is palpable at the apex in long-standing systemic hypertension.

Humphries and McKusick[11] have described very loud late systolic murmurs at the left sternal border or at the apex due to *pericardial roughening*. These murmurs are often initiated by a systolic click and extend to or slightly beyond the second heart sound. A pericardial origin of the murmur is suggested by the history of acute pericarditis and the rather typical T wave changes on the electrocardiogram. The origin of these murmurs is still unclear, but tentatively they can be considered to be innocent.

We have also observed 20 patients with a late systolic murmur in whom a well-documented *acute anterior myocardial* infarction was present. Phonocardiograms recorded in these patients showed that the late systolic murmur ended before closure of the aortic valve. It is postulated that mechanical dysfunction of the anterolateral papillary muscle as a result of the acute infarction is responsible for this murmur.[16] In normal subjects, proper spatial relationships are maintained between the papillary muscles and myocardium, chordae tendineae, and the mitral leaflets. Failure of the scarred papillary muscle to contract during ventricular systole results in bulging of the mitral leaflets during the left ventricular isometric contraction phase. During the ejection phase and with a rapid rise in intraventricular pressure, the mitral leaflet everts into the left atria, which results in mitral regurgitation because of failure of the anterolateral papillary muscle to contract and shorten. The onset of the murmur is expected to occur in early or mid systole during the ejection phase of the cardiac cycle.

Aneurysm of the left ventricle was absent clinically in all 20 patients. These patients with aneurysmal dilatation of the left ventricle may also demonstrate mitral regurgitation, since a portion of the mitral valve is pulled into the left ventricle during systole, separating the leaflets.[16]

Finally, a late systolic murmur has also

been noted in patients with the Marfan syndrome.[9] In these individuals there is a ballooning of the mitral valve leaflets with incompetence during late systole.

Summary

The late systolic murmur is a useful sign of mitral regurgitation. The murmur begins in mid systole, increases in intensity during late systole, and ends with or envelopes aortic valve closure. This murmur is demonstrated by intracardiac phonocardiography in the inflow tract of the left ventricle in the path of the regurgitant jet. Left ventriculograms recorded by cineradiography demonstrate bulging of the septal leaflet of the mitral valve during early systole and Grade II regurgitation confined to late systole. The 8 patients with the late systolic murmur and mitral regurgitation showed only minor pathophysiologic changes which were confirmed by cardiac catheterization.

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Experimental and laboratory reports

The effect of vasoactive antagonists in endotoxin shock

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Injection of lethal quantities of gram-negative bacterial endotoxin into the circulation of dogs results in characteristic vascular changes during the ensuing 30 minute period, including development of systemic arterial hypotension, portal venous hypertension, and an increase in splanchnic vascular resistance.[1] Several naturally occurring vasoactive substances have been implicated in the pathogenesis of endotoxin shock. These include the catecholamines, histamine,[2-7] serotonin,[8,9] and bradykinin.[10]

A possible role for the sympathetic nervous system in endotoxin shock was first suggested by Reilly and associates,[11] who showed that direct injection of minute quantities of endotoxin into splanchnic nerves or autonomic ganglia induced gastrointestinal hemorrhages and necrosis, shock, and death. Penner[12] demonstrated that tetraethylammonium chloride and ergotamine tartrate were able to abort the intestinal lesions induced by endotoxin. Other reports showed that Dibenamine[13,14] prevented the increased vasomotion of endotoxemia.

More recent studies have shown that spinal-cord section does not prevent the hemodynamic changes observed early in endotoxin shock.[15] This has resulted in a shift in emphasis from the sympathetic nervous system to the circulating catecholamines. This concept is supported by the work of Zweifach and associates[2] and Gourzis and associates,[16] who have observed a heightened vascular sensitivity to pressor catecholamines during endotoxemia. Furthermore, regional studies of perfused stomach,[17] small intestine,[1] spleen,[19] kidney,[20,1] and lung[21] indicate that endotoxin increases vascular resistance in these organs and that phentolamine[17,21] can block this rise in resistance. In addition, catecholamine antagonists have been shown to increase survival in endotoxin shock.[16-23]

Other investigators have focused attention on histamine as the primary agent involved in the vascular events of endotoxin shock. Schayer and his collaborators[4,5] have shown that both endotoxin and the histamine liberator Compound 48/80 enhance histidine decarboxylase activity. Hinshaw and associates have described certain similarities in the hemodynamic responses of the dog to histamine, Compound 48/80, and endotoxin.

The dramatic decline in the circulating concentrations of 5-hydroxytryptamine (serotonin) during endotoxin shock[9] and the protective action of serotonin in endo-

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toxemia[8] suggest an important role for this agent.

This investigation describes the early hemodynamic effects of endotoxin in dogs whose response to catecholamines, histamine, acetylcholine, or serotonin was altered pharmacologically.

Methods and materials

Seventy-five mongrel dogs of both sexes which weighed from 10 to 29 kilograms were the subjects of these experiments. Sixty of these animals were anesthetized with pentobarbital sodium (30 mg. per kilogram) administered intravenously. An endotracheal tube was inserted and connected to a positive pressure respirator* with a respiratory minute volume of 2,500 to 4,000 c.c. per minute which maintains a normal pH and pCO_2, thus obviating altered vascular responses to either endotoxin[4] or catecholamines.[2] A left subcostal laparotomy was performed and the splenic artery was exposed. Those branches of the splenic artery which passed to the stomach and the pancreas were ligated. Heparin sodium (10 mg. per kilogram) was injected intravenously and polyethylene tubing was connected through a finger pump† to a metal cannula which was inserted into the splenic artery. Blood flow to the spleen was interrupted for less than 1 minute by this procedure. Flow was fixed in the pump so that pressure in the tubing proximal to the splenic artery would approximate mean systemic arterial pressure recorded from the left femoral artery in 60 animals (Dogs 1-45, 51-65, Table I). In 5 animals (Dogs 61-65) systemic arterial pressure was intentionally reduced 50 per cent by exsanguination. In 5 animals (Dogs 46-50) splenic arterial pressure was purposely maintained at a pressure approximately 50 per cent below systemic arterial pressure.

In 5 animals (Dogs 21-25), morphine sulfate (15 mg. subcutaneously) and chloralose (75 mg. per kilogram intravenously) were employed to induce anesthesia with agents that would not have atropine-like effects and the surgical procedure outlined above was performed.

These 65 animals were divided into 13 groups of 5 dogs each arranged in Table I according to pharmacologic pretreatment, systemic arterial and splenic arterial pressures, or anesthesia. The agents used prior to the injection of endotoxin included the following:

1. Reserpine (CIBA Pharmaceutical Co., Summit, N. J.), 0.2 mg. per kilogram injected intravenously 2 hours before and repeated 1 hour before endotoxin in 5 dogs.

2. Compound 48/80 (Burroughs Wellcome Co., Inc., Tuckahoe, N. Y.), 0.1 mg. per kilogram injected intraperitoneally twice daily for 5 days before endotoxin in 5 dogs. One hour before endotoxin was administered, an additional 0.5 mg. per kilogram was infused intravenously.

3. Atropine sulfate, 0.4 mg. per kilogram injected intravenously 10 minutes before endotoxin. This dose blocked the systemic arterial depressor response to 300 μg of acetylcholine.

4. Pyrilamine maleate (Merck & Co., Inc., West Point, Pa.), 50 mg. per kilogram injected intravenously over a 2 hour period prior to endotoxin. This drug failed to attenuate the systemic arterial depressor response to 100 μg of histamine or the pressor response to 100 μg of norepinephrine administered intravenously. Pyrilamine maleate was used in only 1 dog.

5. Diphenhydramine hydrochloride (Benadryl, Parke, Davis & Co., Detroit, Mich.), 50 mg. per kilogram injected intravenously over a 1 hour period prior to endotoxin. This dose abolished the depressor response to 10 μg of histamine and markedly attenuated the depressor response to 36 and 100 μg of histamine injected intravenously. One animal was pretreated with this drug.

6. N-(2-dimethylamino-2-methyl) ethyl phenothiazine hydrochloride (Phenergan, Wyeth Laboratories, Philadelphia, Pa.), 50 mg. per kilogram injected intravenously over a 1 hour period prior to endotoxin in 3 dogs. This drug abolished the depressor response to 10 μg and markedly attenuated the depressor response to 36 and 100 μg of histamine injected intravenously. The depressor response to 33 μg of isoproterenol was also attenuated, but the depressor response to 100 μg of isoproterenol was unaffected by this phenothiazine derivative. In one of these animals, diph-

*Harvard Apparatus Co., Dover, Mass.
†Sigmamotor Inc., Middleport, N. Y.

Table I. Division of dogs into 13 groups according to pharmacologic pretreatment, anesthesia, and pressures in the systemic and perfusion circuits prior to injection of endotoxin

Group	Dog numbers	Anesthesia	Mean splenic flow (ml./min.)	Mean pressures (mm. Hg): Systemic artery	Mean pressures (mm. Hg): Splenic artery	Pharmacologic pretreatment
I	1–5	Pentobarbital	38	99	110	Control—No agent
II	6–10	Pentobarbital	36	80	94	Reserpine
III	11–15	Pentobarbital	26	83	106	Compound 48/80
IV	16–20	Pentobarbital	40	101	104	Atropine
V	21–25	Morphine and chloralose	41	90	100	Control—No agent
VI	26–30	Pentobarbital	33	70	91	Antihistaminics
VII	31–35	Pentobarbital	29	60	78	Cyproheptadine
VIII	36–40	Pentobarbital	34	104	114	Control—Solvent for phenoxybenzamine
IX	41–45	Pentobarbital	30	45	65	Phenoxybenzamine
X	46–50	Pentobarbital	14	109	65	Control—Low perfusion pressure
XI	51–55	Pentobarbital	26	66	66	Nethalide
XII	56–60	Pentobarbital	35	72	74	DCI
XIII	61–65	Pentobarbital	8	51	74	Control—Low systemic artery

dramine hydrochloride 25 mg. per kilogram was also administered.

7. 1-Methyl-4-(5-dibenzo [a,e]-cycloheptatrienylidene) piperidine (Cyproheptadine, Merck & Co., Inc., West Point, Pa.): 15 to 25 mg. per kilogram injected intravenously over a 1 hour period prior to endotoxin. This drug was dissolved in acetic acid and saline (pH 4.0). In these doses this agent abolished or markedly attenuated the depressor response to 40 and 100 μg of serotonin and markedly attenuated the pressor response to 200 and 400 μg of serotonin injected intravenously in 5 dogs. This serotonin antagonist also converted the depressor response of 33 μg of isoproterenol to a pressor response, markedly attenuated the depressor response to 36 μg of histamine, but had no effect on the pressor response to 33 μg of l-norepinephrine.

8. Phenoxybenzamine hydrochloride (Dibenzyline, Smith, Kline and French Laboratories, Philadelphia, Pa.): 20 mg. per kilogram injected intravenously over a 1 hour period prior to endotoxin in 5 dogs. This substance was dissolved in a solution containing propylene glycol and acetic acid (pH 4.0). In these doses phenoxybenzamine abolished the pressor response to 100 μg of l-norepinephrine and somewhat attenuated the depressor response to 100 μg of histamine.

9. 2-(D-hydroxy-3-isopropyl aminoethyl naphthalene) (Nethalide, Ayerst Laboratories, New York, N. Y.): 30 mg. per kilogram injected intravenously over a 1½ hour period prior to endotoxin. In these doses Nethalide markedly attenuated or abolished the depressor response to 100 μg of isoproterenol, incompletely reduced the depressor response to 100 μg of histamine, and caused some reduction in the pressor responses to 100 μg of l-norepinephrine and serotonin. Nethalide was administered to 5 dogs.

10. 1-(3,4-Dichlorophenyl)-2-isopropylaminoethanol hydrochloride (Aldrich Chemical Co., Inc., Milwaukee, Wisc.) or DCI: 40 to 80 mg. per kilogram injected intravenously over a 1 hour period prior to endotoxin in 5 dogs. In these doses DCI abolished the depressor response to 33 μg of isoproterenol, enhanced the pressor response to 100 μg of l-norepinephrine, somewhat diminished the depressor response to 100 μg of histamine and the pressor response to 400 μg of serotonin.

The lethality of the single lot of endotoxin (*Shigella flexneri* 2A*) employed in these experiments was determined in an additional 10 unanesthetized dogs after preliminary lethality studies in guinea pigs. Half of the animals were killed within 24 hours by a single intravenous injection of 0.6 mg per kilogram. An LD_{50} was employed in these experiments rather than the frequently used endotoxin doses which are many times greater than an LD_{100} for two reasons: the effectiveness of any potential pharmacologic agent in opposing some hemodynamic action of endotoxin could be entirely overwhelmed by massive doses of endotoxin.

After a period of approximately 30 minutes of perfusion of the spleen to allow hemodynamic stabilization, endotoxin was injected into the splenic artery, and mean pressures were monitored in the splenic artery, a mesenteric branch of the portal vein, and the left femoral artery (systemic arterial pressure) by means of a strain gauge transducer connected to a recorder.† Splenic vascular resistance was calculated as the quotient of the mean pressure gradient from the perfused splenic artery to the portal vein and the constant flow, and was expressed as millimeters of mercury per milliliter per minute (P.R.U.). Pressures were obtained at 5 minute intervals for 30 minutes after injection of endotoxin. The well-described "first phase" of endotoxin shock in the dog is complete within this period of time and offers an opportunity of observing the effects of neurohumoral blocking agents on a complex but reproducible hemodynamic entity. The results of a typical experiment are shown in Fig. 1.

It should be noted that we observed certain consistent differences from the usual pattern of changes in pressure which has been reported elsewhere.[1] The increase in portal pressure and the decline in systemic arterial pressure after injection of an LD_{50} of *Shigella flexneri* endotoxin are neither as abrupt nor as profound as those observed with fully lethal doses of *Escherichia coli* endotoxin.

The vascular responses to endotoxin in pharmacologically pretreated dogs were compared by noting the number of animals in each group whose systemic arterial or splenic perfusion pressures changed by more than 10 mm. Hg or whose portal venous pressures increased by at least 4 mm. Hg during the 30 minute period of observation. In addition, statistical comparison of the slopes of pressure and resistance as functions of time during endotoxin shock with or without the various pharmacologic or mechanical treatments was performed employing an analysis of combined hierarchical design,[8] which was programmed for a computer.‡

Results

Control. The injection of 0.6 mg. per kilogram of the endotoxin of *Shigella*

*Difco Laboratories, Detroit, Mich.
†Sanborn Co., Waltham, Mass.
‡RPC 4000, Royal Precision Co., Bethesda, Md.

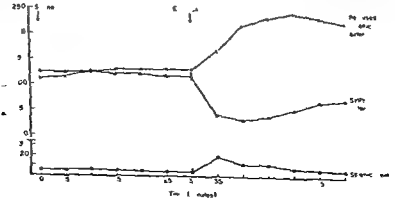

Fig. 1. Typical responses of perfused splenic arterial, systemic arterial, and splenic venous mean pressures to the injection of saline and endotoxin. (U. S. Army photograph.)

flexneri type 2A into the perfusion circuit of 5 control dogs resulted in portal venous hypertension, systemic arterial hypotension, and an increase in both perfusion pressure and splenic vascular resistance. Mean pressure in the portal vein doubled 5 minutes after endotoxin had been administered; pressure in the femoral artery decreased 22 per cent at 10 minutes and 17 per cent at 30 minutes after endotoxin; perfusion pressure increased 36 per cent and the resistance to the flow of blood

*Table II. Comparison of changes in systemic arterial pressure, splenic arterial pressure, portal ... in 6 groups of 5 dogs each**

Group	Time (minutes) 0	5	10	15
Systemic arterial pressure (mm. Hg)				
I Control	99 ± 5	84 ± 11	78 ± 13	78 ± 12
II Reserpine	80 ± 4	50 ± 7	53 ± 4	46 ± 6
III 48/80	83 ± 13	72 ± 8	59 ± 12	57 ± 12
IV Atropine	101 ± 7	80 ± 5	83 ± 7	79 ± 5
V Morphine and chloralose	90 ± 12	76 ± 11	57 ± 14	52 ± 13
VI Antihistaminics	70 ± 7	53 ± 5	49 ± 5	52 ± 4
Splenic arterial pressure (mm. Hg)				
I Control	110 ± 7	121 ± 9	140 ± 6	149 ± 11
II Reserpine	94 ± 5	119 ± 9	140 ± 19	133 ± 15
III 48/80	106 ± 7	117 ± 6	123 ± 7	129 ± 12
IV Atropine	104 ± 11	117 ± 10	131 ± 9	134 ± 10
V Morphine and chloralose	100 ± 4	122 ± 8	150 ± 17	160 ± 16
VI Antihistaminics	91 ± 8	105 ± 7	110 ± 4	112 ± 6
Portal venous pressure (mm. Hg)				
I Control	7 ± 1	14 ± 2	11 ± 1	8 ± 1
II Reserpine	6 ± 1	12 ± 1	10 ± 2	7 ± 2
III 48/80	7 ± 0	10 ± 1	8 ± 1	7 ± 1
IV Atropine	6 ± 1	11 ± 2	9 ± 1	7 ± 1
V Morphine and chloralose	6 ± 1	15 ± 2	12 ± 2	10 ± 1
VI Antihistaminics	8 ± 1	15 ± 1	11 ± 1	9 ± 1
Splenic vascular resistance (P.R.U.)				
I Control	3.20 ± .79	3.30 ± [illegible]	3.89 ± .81	4.31 ± .97
II Reserpine	[illegible] ± [illegible]	3.27 ± .57	3.98 ± .91	3.[illegible] ± .79
III 48/80	3.94 ± .47	4.31 ± .57	4.67 ± .72	5.00 ± .94
IV Atropine	2.70 ± .47	[illegible].97 ± .50	3.44 ± .54	3.58 ± .61
V Morphine and chloralose	2.[illegible]7 ± .59	3.[illegible] ± [illegible]4	4.03 ± .88	4.37 ± .95
VI Antihistaminics	2.7[illegible] ± .67	2.97 ± .65	3.24 ± .63	3.37 ± .68

*The groups are divided according to treatment before endotoxin. p is the probability of no difference in the time sequence of ... arterial pressure declined or splenic arterial pressure increased more than 10 mm. Hg or portal venous pressure increased by at

across the spleen increased 35 per cent at 15 minutes after the injection of endotoxin These results appear in Table II

Reserpine The 5 animals pretreated with reserpine exhibited hemodynamic responses to endotoxin which were similar to those of the control group (Table II) Portal venous pressure increased 100 per cent in 5 minutes systemic arterial pressure declined 34 per cent in 10 minutes perfusion pressure climbed 49 per cent and splenic vascular resistance rose 42 per cent in 15

venous pressure and splenic vascular resistance in response to endotoxin injected at zero time

Time (minutes)—Cont d			N P G	p
20	25	30		
Systemic arterial pressure (mm Hg)				
79 ± 10	82 ± 8	82 ± 7	5/5	—
47 ± 7	48 ± 9	46 ± 11	5/5	n s
54 ± 11	51 ± 11	45 ± 12	5/5	< 01
75 ± 5	76 ± 4	49 ± 5	4/5	n s
52 ± 12	53 ± 13	56 ± 15	5/5	< 05
50 ± 4	51 ± 5	51 ± 4	4/5	n s
Splenic arterial pressure (mm Hg)				
145 ± 10	145 ± 11	147 ± 14	5/5	—
133 ± 16	135 ± 20	137 ± 22	5/5	n s
131 ± 16	130 ± 18	130 ± 21	4/5	n s
132 ± 10	130 ± 10	129 ± 10	5/5	< 05
158 ± 17	158 ± 18	161 ± 18	5/5	n s
108 ± 8	104 ± 9	104 ± 11	5/5	< 001
Portal venous pressure (mm Hg)				
8 ± 1	7 ± 0	7 ± 1	5/5	—
6 ± 1	7 ± 2	7 ± 2	3/5	n s
7 ± 1	6 ± 1	6 ± 1	1/5	< 01
6 ± 1	5 ± 1	5 ± 1	3/5	n s
7 ± 2	6 ± 1	6 ± 2	5/5	n s
8 ± 1	7 ± 1	7 ± 0	5/5	n s
Splenic vascular resistance (P R U)				
4 03 ± 76	4 23 ± 98	4 25 ± 98		—
3 89 ± 79	3 92 ± 84	4 03 ± 95		n s
5 16 ± 1 12	5 16 ± 1 [illegible]	5 15 ± 1 30		n s
3 51 ± 58	3 50 ± 59	3 51 ± 61		< 05
4 41 ± 94	4 50 ± 1 04	4 59 ± 1 03		n s
3 31 ± 75	3 24 ± 78	3 20 ± 79		n s

n press re res ce between each group d ont 1 N P G signifies the umbe f animal pe gr up of 5 wh ch lea t 4 mm Hg with 30 mi tes aft d t xin T b lated re n n valu ± ta dard err of th mea

minutes after endotoxin had been injected.

Compound 48/80. Animals pretreated with Compound 48/80 showed a somewhat less marked response of portal venous pressure and a somewhat greater and more sustained systemic hypotensive response to endotoxin (Table II). Thus, portal venous pressure rose 43 per cent at 5 minutes, systemic arterial pressure fell 29 per cent at 10 minutes and 45 per cent at 30 minutes, and perfusion pressure increased 21 per cent at 15 minutes after the injection of endotoxin.

Atropine. In 5 dogs pretreated with atropine the effects of endotoxin on systemic arterial and portal pressures were not different from those in the control series (Table II). Peak mean portal venous pressure was observed 5 minutes after injection of endotoxin (+83 per cent); systemic arterial pressure declined 20 per cent at 5 minutes after endotoxin and was 17 per cent lower than preinjection values at 10 minutes after endotoxin. Perfusion pressure and splenic vascular resistance exhibited a somewhat less marked increase in response to endotoxin; however, in all 5 animals an increase in perfusion pressure of more than 10 mm. Hg was noted within 30 minutes after endotoxin.

Morphine and chloralose. Since pentobarbital has an anticholinergic effect,[5]

*Table III. Comparison of changes in systemic arterial pressure, splenic arterial pressure, portal in 4 groups of 5 dogs each**

Group	Time (minutes) 0	5	10
	Systemic arterial pressure (mm. Hg)		
VIII Control solvent	104 ± 14	89 ± 19	86 ± 13
VII Cyproheptadine	60 ± 9	50 ± 6	57 ± 8
IX Phenoxybenzamine	45 ± 5	39 ± 4	33 ± 3
X Low perfusion pressure	109 ± 1	82 ± 5	85 ± 5
	Splenic arterial pressure (mm. Hg)		
VIII Control solvent	114 ± 8	122 ± 10	135 ± 7
VII Cyproheptadine	78 ± 9	86 ± 9	85 ± 9
IX Phenoxybenzamine	65 ± 8	68 ± 10	70 ± 11
X Low perfusion pressure	65 ± 7	74 ± 6	94 ± 11
	Portal venous pressure (mm. Hg)		
VIII Control solvent	6 ± 2	15 ± 3	12 ± 1
VII Cyproheptadine	10 ± 0	13 ± 1	11 ± 1
IX Phenoxybenzamine	6 ± 1	6 ± 1	6 ± 1
X Low perfusion pressure	7 ± 1	15 ± 0	11 ± 1
	Splenic vascular resistance (P.R.U.)		
VIII Control solvent	3.74 ± .87	3.85 ± .88	4.22 ± .87
VII Cyproheptadine	2.60 ± .63	2.77 ± .59	2.80 ± .60
IX Phenoxybenzamine	2.06 ± .35	2.15 ± .38	2.20 ± .39
X Low perfusion pressure	4.08 ± .24	4.15 ± .41	5.98 ± .6

*The groups are divided according to treatment before endotoxin. The control group received an infusion of the solvent used to dissolve ... distance between each group and control. N.I.G. signifies the number of animals per group of 5 in which systemic arterial pressure ... within 30 minutes after endotoxin. The numbers tabulated are mean values ± standard error of the mean.

animals were anesthetized with morphine and chloralose for purposes of comparison with the control and atropine treated groups The injection of endotoxin in these dogs produced hemodynamic events similar to those of either control or atropine treated dogs (Table II) Portal venous pressure increased 150 per cent at 5 minutes and was still 100 per cent above preinjection pressures at 10 minutes after injection Pressure in the splenic artery increased 60 per cent and vascular resistance rose 58 per cent at 15 minutes after endotoxin was administered Systemic arterial pressure declined 40 per cent at 15 minutes after endotoxin

Antihistaminics Pretreatment of 5 dogs with sizeable doses of antihistaminics did not alter the pattern of systemic or portal hemodynamic responses but reduced somewhat the perfusion pressure response to endotoxin (Table II) Portal venous pressure increased 87 per cent at 5 minutes systemic arterial pressure declined 30 per cent at 10 minutes splenic arterial pressure increased 23 per cent and splenic vascular resistance increased 20 per cent at 15 minutes after endotoxin was injected However all 5 animals exhibited an increase in splenic arterial pressure of 10 mm Hg or more during the period of observation

venous pressure and splenic vascular resistance in response to endotoxin injected at zero time

Time (minutes)—Cont'd 15	20	25	30	Δ P G	*p*
Systemic arterial pressure (mm Hg)					
87 ± 12	86 ± 15	83 ± 15	85 ± 13	5/5	—
50 ± 7	46 ± 6	43 ± 6	40 ± 6	5/5	n s
31 ± 3	29 ± 4	25 ± 3	20 ± 4	5/5	< 05
89 ± 5	87 ± 3	89 ± 3	90 ± 3	5/5	n s
Splenic arterial pressure (mm Hg)					
150 ± [illegible]	152 ± 12	147 ± 12	147 ± 11	5/5	—
81 ± 8	76 ± 9	75 ± [illegible]	53 ± 9	1/5	< 001
[illegible] ± 10	63 ± 9	58 ± 7	55 ± 7	1/5	< 001
95 ± 11	86 ± 11	83 ± 10	84 ± 10	4/5	n s
Portal venous pressure (mm Hg)					
9 ± 1	7 ± 1	7 ± 1	6 ± 1	3/5	—
10 ± 1	8 ± 1	8 ± 1	7 ± 1	3/5	n s
5 ± 1	5 ± 1	4 ± 1	3 ± 1	0/5	< 001
9 ± 1	8 ± 1	8 ± 0	8 ± 1	5/5	n s
Splenic vascular resistance (P R U)					
4 80 ± 99	4 91 ± 98	4 67 ± [illegible]	4 75 ± 87		—
2 72 ± 63	2 6? ± 66	2 64 ± 77	2 58 ± 74		< 001
2 19 ± 38	2 0? ± 34	1 88 ± 31	1 48 ± 28		< 001
[illegible] 11 ± 69	5 53 ± 69	5 42 ± 78	5 49 ± 80		n s

ph xybenzamine a d Cyproh ptadin p s the pr babil ty of no diff rence the time seq enc of ch ges n pre sure re-
declined or sple ic arter l pressure increased more th n 10 mm Hg or port l venous pressure increased by t least 4 mm H

Cyproheptadine The use of Cyproheptadine in 5 dogs was attended by a marked decrease in the magnitude of changes in splenic arterial pressure after the injection of endotoxin The increases in splenic arterial pressure and splenic vascular resistance were 10 and 7 per cent respectively at 5 minutes and 9 and 8 per cent respectively at 10 minutes after endotoxin Systemic arterial pressure had declined 16 per cent from preinjection values at 5 minutes 13 per cent at 10 minutes and 33 per cent at 30 minutes after endotoxin These results appear in Table III

Control solvent The 5 dogs pretreated with the solvent used as a vehicle for phenoxybenzamine and Cyproheptadine exhibited hemodynamic alterations quite similar to those of the first control group (Table III)

Phenoxybenzamine Prior infusion of phenoxybenzamine induced marked alteration of the splanchnic vascular responses to endotoxin (Table III) There was no increase in mean portal venous pressure and only an 8 per cent rise in perfusion pressure and a 7 per cent increase in vascular resistance at any time during the 30 minute period of observation The pattern of response in these dogs was significantly different from that of control animals (p = < 001 for either of the pres

*Table IV Comparison of changes in systemic arterial pressure splenic arterial pressure portal in 4 groups of 5 dogs each**

Group	Time (minutes) 0	5	10	15
	Systemic arterial pressure (mm Hg)			
I Control	99 ± 5	[illegible] ± 11	78 ± 13	[illegible] ± 12
XI Nethalide	66 ± 8	60 ± 7	60 ± 8	60 ± 9
XII DCI	2 ± 4	6? ± 9	67 ± 8	63 ± 7
XIII Hemorrhage	51 ± 5	43 ± 4	40 ± 5	44 ± 5
	Splenic arterial pressure (mm Hg)			
I Control	110 ± 7	121 ± 9	140 ± 6	149 ± 11
XI Nethalide	66 ± 6	90 ± 10	101 ± 13	91 ± 13
XII DCI	74 ± 7	118 ± 8	136 ± 9	125 ± 11
XIII Hemorrhage	74 ± 7	?9 ± 6	?6 ± 6	76 ± 8
	Portal venous pressure (mm Hg)			
I Control	7 ± 1	14 ± 2	11 ± 1	8 ± 1
XI Nethalide	6 ± 1	11 ± 2	9 ± 1	8 ± 1
XII DCI	6 ± 0	11 ± 0	9 ± 1	7 ± 1
XIII Hemorrhage	6 ± 1	9 ± 1	8 ± 1	7 ± 0
	Splenic vascular resistance (P R U)			
I Control	3 70 ± 9	3 30 ± 87	3 89 ± [illegible]	4 31 ± 9
XI Nethalide	2 61 ± 63	3 25 ± [illegible]	3 66 ± 50	3 31 ± 49
XII DCI	2 35 ± 64	3 59 ± 91	4 29 ± 1 01	4 03 ± 1 06
XIII Hemorrhage	8 53 ± 64	8 79 ± 65	8 ?8 ± 57	8 [illegible] ± 53

*The groups are divided according to treatment before endotoxin p the probability of no difference in the time sequence of changes in arterial pressure declined or c arterial pressure increased more than 10 mm Hg or portal ven u pres ncreased by at

sures or resistance) Systemic arterial pressure exhibited a steady decline over the period of observation at 10 minutes after endotoxin the decrease averaged 27 per cent and at 30 minutes had reached a level 55 per cent below preinjection pressures It should be noted also that phenoxybenzamine induced profound changes in these animals before endotoxin was administered Pressures in the perfusion circuit and in the femoral artery were approximately 50 per cent lower than pressures obtained in control dogs before endotoxin was injected

Low perfusion pressure In a series of 5 dogs whose perfusion pressures were maintained at levels comparable to pressures in the phenoxybenzamine treated group before injection of endotoxin the responses of perfusion pressure and splenic vascular resistance to endotoxin were similar to events observed in control dogs (Table III) However these splanchnic responses differed significantly from the sequence recorded from dogs treated with phenoxybenzamine (p = < 001 for pressure and < 001 for resistance) Portal venous and systemic arterial pressures were not significantly different from those of control dogs in this group

Methalide The splanchnic vascular responses to endotoxin in animals pretreated

venous pressure and splenic vascular resistance in response to endotoxin injected at zero time

Time (minutes)—Cont d			N P G	p
20	25	30		
Systemic arterial pressure (mm Hg)				
79 ± 10	82 ± 8	87 ± 7	5/5	—
67 ± 9	62 ± 8	62 ± 8	2/5	< 05
61 ± 8	63 ± 7	62 ± 4	2/5	< 05
45 ± 5	47 ± 5	39 ± 5	4/5	< 05
Splenic arterial pressure (mm Hg)				
145 ± 10	145 ± 11	147 ± 14	5/5	—
86 ± 13	85 ± 13	85 ± 14	4/5	< 001
116 ± 12	112 ± 14	108 ± 14	5/5	< 001
77 ± 9	73 ± 9	72 ± 8	4/5	—
Portal venous pressure (mm Hg)				
8 ± 1	7 ± 0	7 ± 1	5/5	—
7 ± 1	7 ± 1	6 ± 1	4/5	n s
6 ± 1	6 ± 1	6 ± 1	5/5	n s
7 ± 0	6 ± 1	6 ± 0	3/5	n s
Splenic vascular resistance (P R U)				
4 03 ± 76	4 23 ± 98	4 25 ± 98		
3 73 ± 54	3 14 ± 59	3 34 ± 86		< 001
3 79 ± 1 06	3 68 ± 1 09	3 56 ± 1 04		< 001
8 75 ± 49	8 27 ± 53	8 28 ± 46		

Pr ssur res tance between ach g up nd cont ol N P G g (et the numbe of nimal pe gr up f 5 n which y t m c lea t 4 mm Hg w th 30 minutes aft dot xin The numbe s b lat d mea ± t nda d of th m

with Nethalide resembled events in control animals except for a more rapid return of splenic arterial pressure and resistance toward base line levels. The changes in systemic arterial pressure after injection of endotoxin exhibited a time course similar to that in control animals; however, the magnitude of fall in pressure was considerably reduced in these animals. In the Nethalide group, systemic pressure declined 10 per cent at 10 minutes and was only 6 per cent below starting values at 30 minutes after the injection of endotoxin. By contrast, systemic arterial pressure had fallen 22 per cent at 10 minutes and 10 per cent at 30 minutes after endotoxin in the control dogs. Of the 5 animals pretreated with Nethalide, only 2 manifested a decline in systemic arterial pressure exceeding 10 mm. Hg within 30 minutes after the injection of endotoxin. Of the 15 dogs which could be considered to be controls (Groups I, V, and VIII, Table I), all showed a drop in systemic arterial pressure of more than 10 mm. Hg within the 30 minutes after endotoxin. These results appear in Table IV.

DCI. The animals which received the beta receptor antagonist DCI exhibited hemodynamic responses to endotoxin similar to those observed in the group given Nethalide (Table IV). Thus, 3 of these dogs did not manifest the early hypotensive response to endotoxin, and the group had a mean fall in systemic arterial pressure of 14 per cent at 5 minutes and 7 per cent at 10 minutes after endotoxin was injected. The perfusion pressure responded to endotoxin in a manner similar to that in animals treated with Nethalide: a marked increase maximal at 10 minutes followed by a return toward preinjection pressures.

Hemorrhage. Since systemic arterial pressure was materially reduced in many of the groups prior to the administration of endotoxin (Table I), partial exsanguination was employed to provide a hypotensive group for comparison purposes. Systemic arterial pressure fell 22 per cent at 10 minutes after endotoxin in this group (Table IV). Four of these animals exhibited a fall in pressure of more than 10 mm. Hg within 10 minutes after endotoxin was injected.

Discussion

The results of this study indicate that the abrupt increase in portal venous pressure and the rise in splanchnic vascular resistance induced by endotoxin are essentially abolished by prior treatment with an alpha receptor (pressor) antagonist, phenoxybenzamine. In addition, in a majority of dogs the profound early fall in systemic arterial pressure seen in endotoxin shock was greatly attenuated by prior treatment with the beta receptor (depressor) antagonists, Nethalide and DCI. Splanchnic vascular responses to endotoxin were somewhat modified by prior administration of Cyproheptadine, Compound 48/80, or antihistaminics. There were no consistent changes in the early hemodynamic events of endotoxemia in animals pretreated with reserpine, atropine, or morphine and chloralose.

The nature of this study introduces certain limitations in the interpretation of these findings. The obvious technical shortcomings of this investigation include the use of the dog as the experimental model for endotoxin shock. This animal exhibits hemodynamic responses to endotoxin unlike those of the monkey, rabbit, and cat.[27] The use of deep pentobarbital anesthesia induces a hyporeactive nervous state, particularly with respect to the parasympathetic nervous system. The extensive surgery involved and the use of a mechanical pump which traumatizes formed blood elements add further variables which compromise the physiologic condition of the animal. Finally, the doses of pharmacologic agents required to block specific neurohumoral substances were of such magnitude as to induce toxicity in the animals, to antagonize other neurohumoral substances, and to limit severely any clinical inferences.

Both the attenuation of portal hypertension and the increase in splenic vascular resistance by phenoxybenzamine implicates alpha adrenergic vascular stimulation in the mechanism of these early hemodynamic changes of endotoxemia. Furthermore, the pattern of systemic arterial pressure in the animals pretreated with phenoxybenzamine was significantly different from that of the control group; the abrupt decline in arterial pressure did not

occur in the group which received phenoxybenzamine although there was a progressive profound fall in the pressures over 30 minutes This is consistent with the explanation offered by the Minnesota group[24] that splanchnic vascular pooling is responsible for the acute development of hypotension during endotoxin shock in dogs In addition the reports that phentolamine induces a similar response to endotoxin in the circulation of the stomach[17] and kidney[21] during endotoxemia support our findings

Systemic arterial hypotension after injection of endotoxin was nearly abolished in a majority of dogs pretreated with the beta adrenergic receptor inhibitors Nethalide and DCI despite the occurrence of typical splanchnic vascular changes This suggests a possible role for beta receptor stimulation in endotoxin shock perhaps by endotoxin itself pressor catecholamines or an unidentified depressor catecholamine Another explanation which might be considered relates to the striking parallelism in the hemodynamic effects of epinephrine and endotoxin Both compounds induce splanchnic pooling [8-10] a diminished circulating blood volume [22,31] splanchnic [1,32] renal [20,33] and cutaneous[11,34] vasoconstriction and dilate the circulatory beds in the heart [34,35] with an over all reduction in total peripheral resistance [36,37] Furthermore plasma levels of epinephrine are increased early in endotoxin shock with a less marked effect on the levels of norepinephrine [6] The beta receptor antagonists enhance the *pressor effects of epinephrine* [38] thereby lessening the difference between the vasoactive actions of epinephrine and norepinephrine The over all effect of Nethalide or DCI could *therefore* be an increase in total peripheral resistance in response to epinephrine the major catecholamine released in the early phase of endotoxemia This could explain the paradox of an amelioration of systemic arterial hypotension in the face of splanchnic vasoconstriction observed in the dogs to which Nethalide or DCI was administered

Since the starting systemic arterial blood pressure in animals treated with phenoxybenzamine Nethalide DCI antihistaminics and Cyproheptadine was considerably lower than in control animals a series of dogs whose arterial pressures were decreased by partial exsanguination was used as a control hypotensive group In these animals the early response of systemic arterial pressure to endotoxin was diminished and the depressor response to isoproterenol was also diminished However it is probable that partly exsanguinated dogs would exhibit a somewhat different initial response to the shocking effects of endotoxin since plasma levels of catecholamines would be elevated (as the extremely high splenic vascular resistance in the exsanguinated dogs indicates) and plasma levels of steroids would be increased just before the administration of endotoxin Furthermore the groups of dogs receiving antihistaminics Nethalide and DCI with comparable initial blood pressures exhibited different responses to endotoxin At 10 minutes after endotoxin the declines in pressure were −21 −6 and −5 mm Hg in these 3 groups respectively This suggests that the amelioration of endotoxin induced hypotension observed in dogs treated with Nethalide DCI and phenoxybenzamine was due in large part to the pharmacologic agent used

It is difficult to explain the diminished response of perfusion pressure to endotoxin *in animals pretreated* with Cyproheptadine and antihistamines and the reduced portal venous changes in animals receiving *Compound 48 80* Other substances which oppose the actions of serotonin and histamine have also been reported to change certain of the vascular responses to endotoxin [2,40] Pretreatment of dogs with reserpine Compound 48 80 atropine morphine and chloralose and antihistaminic drugs did not diminish the hypotensive response to *endotoxin* Although reserpine is a potent postganglionic adrenergic blocking agent[41] and depletes tissues of catecholamines and serotonin studies in this laboratory *indicate* that measurable concentrations of catecholamines in the plasma are present in reserpine treated dogs and that endotoxin can induce elevations of the levels of epinephrine in the plasma of these *animals* In addition the increase in renal vascular resistance induced by endotoxin *is not blocked by* reserpine [1] Compou

48 80 is a potent histamine liberator however in studies in progress no difference has been observed in the concentrations in plasma of catecholamines histamine or serotonin between control animals and dogs pretreated with Compound 48 80 Furthermore the animals treated with Compound 48 80 exhibit changes in these plasma neurohumoral agents in response to endotoxin which do not differ from those of control dogs It appears that reserpine and Compound 48 80 are not totally effective agents in depleting body stores of neurohumoral substances The specificity of atropine for the parasympathetic system and the essential lack of difference between atropine treated animals and dogs anesthetized with either pentobarbital or morphine and chloralose implies a minor role for cholinergic vascular receptors in the early phase of endotoxin shock

There are two possible explanations for the apparent discrepancy between our findings and the report by Tsagaris and associates[40] in which they showed that antihistaminics effected some amelioration of the hypotension induced by lethal doses of *Escherichia coli* endotoxin First it may be that the endotoxin of *Escherichia coli* induces hypotension through activation of neurohumoral systems different from those stimulated by *Shigella flexneri* endotoxin Second the explanation could relate to the amount of endotoxin injected According to Spink (personal communication) plasma concentrations of histamine are markedly elevated within 1 minute after the injection of amounts of endotoxin in excess of the lethal dose We have not found increases in plasma histamine values after sublethal amounts of *Escherichia coli* endotoxin (unpublished observations) It is possible that a histamine component is superimposed on the basic effects of endotoxin when massive doses are injected and under these conditions antihistaminics might exert partial attenuation of the hemodynamic effects of endotoxin

Although the foregoing discussion has underscored the participation of catecholamines in endotoxin shock the complexity of the pathologic state implies the interaction of many neurohumoral systems

Summary

The effect of pharmacologic antagonists on vascular pressures in the perfused splenic artery a branch of the portal vein and in a systemic artery were monitored for 30 minutes after the injection of an LD_{50} of *Shigella flexneri* endotoxin In control animals the injection of endotoxin was followed by a rapid increase in splenic arterial pressure portal venous pressure and vascular resistance across the spleen Systemic arterial pressure exhibited an abrupt decline after the injection of endotoxin Pretreatment of dogs with the alpha vascular receptor antagonist phenoxybenzamine prevented the increase in portal venous pressure and markedly attenuated the rise in splenic perfusion pressure Pretreatment of dogs with either of two beta vascular receptor antagonists Nethalide or DCI ameliorated the fall in systemic arterial pressure without diminishing the splanchnic vascular responses to endotoxin The serotonin antagonist Cyproheptadine diminished the increase in splenic perfusion pressure after endotoxin Atropine reserpine Compound 48/80 or antihistaminics did not diminish the hypotensive response to endotoxin although the increase in portal venous pressure was less marked in dogs to which Compound 48 80 had been administered and perfusion pressure did not increase as markedly in animals pretreated with antihistaminics

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The effects of abnormal concentrations of the serum electrolytes on left ventricular function in the intact animal

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When an abnormal concentration of one of the serum electrolytes is encountered in a patient with a general circulatory disorder, it is of interest to know whether a direct effect of the electrolyte abnormality on cardiac functional capacity may be contributing to the circulatory impairment. Considerable information has accumulated in regard to the effects of brief variations of the ionic composition of the nutrient medium on the force of contraction of the isolated myocardium.[1-8] However, almost no data are available concerning the direct effects of prolonged changes in the serum electrolyte pattern on ventricular functional capacity in the intact human subject or the experimental animal because of methodologic problems of two types. First, studies have been conducted over brief periods of time and under resting conditions when impairment of cardiac function is less evident than when a circulatory load is imposed. Second, the measurements used have not distinguished between inotropic effects and those mediated by alterations of venous return or arterial blood pressure.

Recently, a method has been developed[9] by which left ventricular contractile strength can be assessed during a circulatory load in the intact animal. During graded obstruction of the ascending aorta, a left ventricular "pressure function" curve is obtained which relates peak systolic to end-diastolic pressure. The curve is highly reproducible both during steady circulatory states and during large changes in cardiac output and blood pressure. Displacements of the curve may be expressed in terms of the $P_{12.5}$ index, which is the left ventricular peak systolic pressure at an end-diastolic pressure of 12.5 mm. Hg. This index is directly related to the maximum peak systolic pressure observed during complete aortic obstruction.[9]

Displacements of the pressure function curves are noted after procedures which are known to affect the myocardium directly, such as the administration of sympa-

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thetic drugs or the induction of severe anoxia and alterations in the curves parallel those of concomitant Starling ("flow function") curves in open-chest dogs. Furthermore, changes in the P_{12} index correlate well with changes in isometric contractile force measured with a strain-gauge arch.[9] Therefore, although the pressure function curve cannot be considered to be the equivalent of a length-tension diagram, it may be used to indicate inotropic interventions without thoracotomy and without confusion with associated alterations in systemic blood flow, ventricular filling pressure, or aortic blood pressure.

Another measurement which can be made in the intact animal and which reflects a different aspect of the contractile function of the left ventricle is the maximum rate of rise of intraventricular pressure (dp/dt Max).[10,11] Changes in this index have been considered to be useful in indicating inotropic interventions, although the index is also influenced by changes in ventricular filling pressure, heart rate, and arterial pressure.

In the present study the effects of prolonged changes in the serum pH and serum concentrations of calcium ([Ca]), sodium ([Na]), and potassium ([K]) on ventricular function were assessed in the intact anesthetized dog, using the pressure function curve and the maximal rate of rise of intraventricular pressure as explained above. The effect of a change of heart rate per se on the pressure function curve was studied in order to evaluate results associated with changes in heart rate. The possibility that epinephrine discharge might have contributed to the response of the heart to changes in serum [K] or pH was explored using dichloroisoproterenol (DCI) to block the β receptor (hence cardiac) effects of epinephrine.[13,14]

Methods

Each of 58 mongrel dogs on a standard chow diet, weighing between 10 and 22 kilograms, was fasted overnight and then anesthetized with 6 mg. per kilogram of Dial urethane. The trachea was intubated using a cannula with an inflatable balloon cuff for administration of 100 per cent oxygen delivered by an open-circuit respirator which contained a "demand" valve in amounts dictated by the animal's own respiratory drive. In order to obtain left ventricular pressure function curves, a special metal cannula equipped with an inflatable rubber balloon for graded obstruction of the ascending aorta was inserted into the left ventricle via the left carotid artery. Catheters were inserted via the femoral vessels for determinations of intravascular pressures and cardiac output and for administration of appropriate electrolyte solutions. These methods have been described previously in detail.[9] The maximum rate of rise in left ventricular pressure (dp/dt Max) was derived directly by electronic differentiation of the ventricular pressure curve, using a special amplifier.* The differential tracing was calibrated in each experiment by comparison with one or more direct measurements of the maximum slopes of the ascending portions of left ventricular pressure curves recorded simultaneously on a multichannel recorder* at 50 to 100 mm. per second.

In 6 dogs, pressure function curves and other measurements were obtained during consecutive alterations of heart rate induced by stimulation of the distal cut end of the right vagus nerve at a duration of 6 msec., frequency of 8 per second, and voltages between 0.2 and 1.5 volts.

In 2 dogs the vagus nerve was separated from adjacent sympathetic fibers by dissection in the region of the stellate ganglion. The experimental results obtained by stimulation of the isolated nerve, after all other fibers had been cut, were the same as those obtained using the cut cervical trunk.

In 58 dogs, changes in the serum electrolytes were induced by the infusion of one or more of the electrolyte solutions listed in Table I or by artificial dialysis with a Kolff artificial kidney† which was primed with dog blood and attached to large-bore cannulas inserted into the femoral vein and artery. The dialysis bath was either potassium free or contained sodium at a concentration of 100 mEq. per liter. Other

*Special amplifier and recorder made by Electronics for Medicine Inc., White Plains, N. Y.

†The authors are indebted to Dr. [illegible] and Dr. [illegible] Theodore Phillips for their assistance in the use of the artificial kidney in these experiments.

ions were added at the concentrations found in normal extracellular fluid The experimental protocol was as follows (a) During a control period intravascular pressures and cardiac output were measured and left ventricular pressure function curves were obtained 3 to 6 times at intervals of about 5 to 15 minutes dp dt Max was determined in the absence of aortic obstruction just before each pressure function curve was obtained (b) After the control period one of the afore mentioned electrolyte solutions was infused or artificial dialysis was carried out after which all measurements were repeated 2 to 5 times at intervals of 5 to 15 minutes (c) Another solution was infused usually selected to counteract the electrolyte distortion produced by the first solution and all measurements were again repeated 2 to 5 times (d) In 13 dogs dichloroisoproterenol (DCI) was administered (6 mg per kilogram) after the initial control period and before the first infusion and all measurements were repeated 3 to 4 times (e) Blood was withdrawn at appropriate points to follow the changes in blood electrolytes induced by each infusion The withdrawn blood was replaced by the injection of an equal volume of dextran so as to avoid depletion of the blood volume

Chemical analyses of blood or serum Sodium and potassium were measured by standard flame photometry pH was determined with a Beckman glass electrode calcium was measured by the complexometric method using trisodium ethylenediamine tetraacetic acid (EDTA)[15] the blood hematocrit was determined in capillary tubes by a standard method

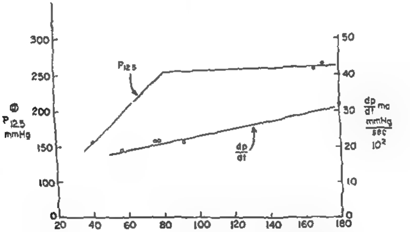

Fig 1 Changes in the $P_{12.5}$ index and dp/dt Max (see text and Fig 3 for definitions of these abbreviations) during repeated episodes of bradycardia induced by vagal stimulation in 2 representative experiments

Table I Solutions infused

	Electrolyte	*Concentration*	*Rate of administration*	*Total mEq given*
A	NaCl	870-1 740 mEq /L	17 0 mEq /min	14 0 mEq /kg
B	NaCl	43-87 mEq /L	1 5 mEq /min	3 5 mEq /kg
C	KCl	150 mEq /L	0 7 mEq /min	2 4 mEq /kg
D	HCl	300 mEq /L	3 3 mEq /min	4 6 mEq /kg
E	$NaHCO_3$	500 mEq /L	8 0 mEq /min	4 [illegible] mEq /kg
F	Na-EDTA	1 500 mg %	34 mg /min	100 mg /kg
G	$CaCl_2$	1 100 mg %	44 mg /min	75 mg /kg
H	Ca-EDTA	1 500 mg %	61 mg /min	100 mg /kg
I	Mannitol	1 400 mM /L	14 7 mM /min	14 4 mM /kg

Results

1 *Effect of heart rate on ventricular function curve and upon dp/dt Max (Fig 1)* Rapid large reductions in heart rate were induced by brief vagal stimulation in 6 dogs Although dp/dt Max was closely related to heart rate the ventricular function curve was rate-dependent chiefly at values below 80 beats per minute Above this rate the curve was only mildly affected by changes in rate of the largest magnitude observed after electrolyte infusions in this study (a reduction of 40 beats per minute in one of the dogs with severe acidosis) These changes in ventricular function are attributed to changes in rate alone since previous studies have shown that vagal stimulation is without effect on the ventricles paced at a constant rate[16] Above a heart rate of 80 beats per minute an

Table IIA Left ventricular functions before and after changes in the serum electrolytes[1]

Experimental group	*Solution infused (see Table I)*	*Number of dogs*	*Range of serum electrolyte values after infusion*	*Average changes*[2]		
				$P_{12.5}$ index[3] *(mm Hg)*	*dp/dt Max*[4] *mm Hg/sec* *(×10²)*	*dp/dt Max*[4] / *EDP*[5] *mm Hg/sec / mm Hg* *(×10¹)*
Controls[8]	None	26		(189)[2] +1 +10	(20 0) −1 0 ± 2 7	(44) +3 ±29
Hypocalcemia	Na_3-EDTA[6]	7	3 8–6 0 mg %	−53 ±52	−7 7 ± 6 1	−19 ±19
Hypercalcemia	$CaCl_2$	5	23–50 mg %	+116 ±47	+25 8 ±15 8	+75 ±51*
Acidosis	0 5N HCl					
No DCI		4	7 02–7 23 units	−5 ±18	−2 8 ± 3 9	+2 ±24
No DCI		5	6 80–6 92 units	−53 ±20	−6 7 ± 5 9	−35 ±40+
After DCI		4	6 97–7 11 units	−5 ±2	−0 7 ± 2 4	−6 ±11
Alkalosis	0 5N $NaHCO_3$	3	7 56–7 58 units	−5 ±16	+5 ±14+	+21 ±32
Hypokalemia	Dialysis	2	2 1– 2 5 mEq /L	+19 —	−0 6 —	+6 —
Hyperkalemia	Isotonic KCl					
No DCI		8	8 4–11 5 mEq /L	−3 ±15	+1 1 ± 3 1	−4 ±12
After DCI[7]		4	8 6–10 5 mEq /L	−14 ±2	+3 5 ± 5 4+	−11 ±11
Hyponatremia	Dialysis ½% NaCl	6	116–130 mEq /L	−8 ±7	−1 1 ± 4 8	+2 ±5
Hypernatremia	Mannitol 5–10 per cent NaCl	10	163–218 mEq /L	−6 ±16	+2 6 ± 5 4+	+6 ±11
DCI (6 mg /kg)[8]	None	9		+31 ±71*	+4 8 ± 4 9	+29 ±22

1 All experimental values obtained at least 30 minutes after infusion of electrolyte solution
2 Changes expressed as the differences between experimental values and initial values in the same animals Control values are the spontaneous changes from initial values (in parentheses) in the absence of an experimental procedure Average changes given with standard deviations from the means Statistical evaluation *= $p < .01$ += $.01 < p < .05$
3 $P_{12.5}$ index = Left ventricular peak pressure at an end diastolic pressure of 12 5 mm Hg
4 dp/dt Max = Maximum rate of rise in left ventricular pressure
5 EDP = Left ventricular end diastolic pressure
6 Na_3EDTA = Trisodium ethylenediamine tetra acetic acid
7 Values during hyperkalemia after *DCI* compared with values after *DCI* alone
8 DCI = Dichloroisoproterenol

alteration of 10 beats per minute induced about 1 per cent change in the P_1 index and about a 4 per cent change in dp/dt Max (Fig 1)

2 *Effects of DCI* (*Table II Figs 4 7*) DCI was administered to 9 dogs in a dose of 6 mg per kilogram In every case the drug sharply augmented the P_1 index dp/dt Max the heart rate and the cardiac output and reduced arterial and left ventricular end-diastolic blood pressure The arterial blood pressure fell and marked cutaneous flushing was observed These changes indicated a fall in systemic arteriolar resistance and a positive inotropic effect on the myocardium which was unexpected on the basis of a previous report [11] The effects lasted for 1½ to more than 3 hours after administration of the drug

3 *Effects of alterations in serum electrolytes* Changes in the numerical equivalent (P_1 value) of the pressure function curve of the maximal rate of rise in the left ventricular pressure curve (dp/dt Max) and of associated hemodynamic and chemical data from 58 experiments are summarized in representative Figs 1 5 and in Table II The values used for Table II were based on the averages of 2 to 5 individual measurements during each period of observation and all values within 30 minutes after each experimental infusion were omitted in order to avoid the immediate effects of changes in blood volume and of epinephrine discharge which might have been induced by some of the infusions

Control values represent spontaneous changes from initial values (in parentheses) in the absence of an experimental procedure They were obtained during periods similar in duration to those used for the infusion experiments

CHANGES IN SERUM Ca (TABLE II FIGS 2 3) The pressure function curve was markedly altered by hypocalcemia and hypercalcemia (Fig 2) The P_1 value decreased as the serum calcium concentration fell below 7 0 mg per cent (Figs 2 and 3) and increased progressively with hypercalcemia up to a value of 20 mg per cent (Fig 2) The arterial blood pressure and heart rate fell with hypocalcemia and rose with hypercalcemia as did the maximum rate of rise in the ventricular pressure curve (dp dt Max) (Fig 3) and its derived index $\frac{dp/dt}{EDP}$ Max (Table II)

Table IIB Left ventricular functions before and after changes in the serum electrolytes[1]

Experimental group	*Average changes and statistical evaluation*									
	Cardiac output (L /min)		*EDP (mm Hg)*		*Heart rate per minute*		*Mean systolic blood pressure (mm Hg)*		*Stroke work (Gm meters)*	
Control[2]	(1 9)[3]		(4 5)		(125)		(138)		(26)	
	−0 1	±0 3	0	±1 5	0	±7	−3	±8	−4	±4
Hypocalcemia	0	±0 5	+1 9	±2 1	−15	±24	−23	±10	−2	±6
Hypercalcemia	+1 3	±0 7	−2 2	±3 3	+14	±6*	+39	±27	+25	±11
Acidosis										
No DCI	−0 3	±0 3	+1 0	±0 8	+4	±13	−8	±18	−5	±4
No DCI	−0 3	±0 2	+1 6	±2 1*	−28	±16	−12	±22	−2	±5
After DCI	+0 3	±0 7	+0 6	±2 3	−15	±18	+15	±24	+10	±19
Alkalosis	−0 1	±0 8	−0 4	±0 4	0	±10	+2	±7	+4	±9
Hypokalemia	−0 1	—	−2 4	—	−12	—	−10	—	−1	—
Hyperkalemia										
No DCI	+0 3	±0 9	+0 6	±1 3	−15	±23	+10	±16	+11	±15
After DCI[5]	+0 8	±1 1	+0 8	±0 7	−16	±29*	+15	±14	+21	±19
Hypernatremia	+0 4	±0 7	+0 3	±1 4	+13	±15	−7	±5	+1	±8
Hyponatremia	−0 2	±0 7	−0 3	±1 5	0	±8	−9	±16	−4	±9
DCI (6 mg /kg)	+0 6	±0 3	−2 1	±2 3	+18	±18	−24	±19	−2	±5

For footnotes see Table IIA

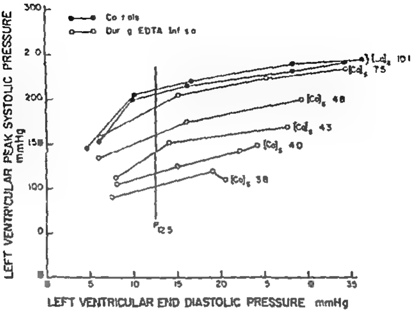

Fig. 2. Ventricular pressure function curves at progressive degrees of hypocalcemia due to the infusion of EDTA.

The cardiac output and ventricular stroke work were not changed by hypocalcemia but were increased during hypercalcemia over a period of time as long as 2 hours (Fig. 3). Left ventricular end-diastolic pressure varied reciprocally with changes in [Ca] (Table II). The electrocardiogram showed reversible S-T and T abnormalities at high levels of [Ca] (Fig. 3), but was normal over the range of [Ca] values between 3.0 and 12.0 mg. per cent, where marked changes in ventricular contractile capacity were noted. The changes in the $P_{12.5}$ index, dp/dt Max., and cardiac output caused by hypercalcemia were also observed in one dog after β receptor blockade by DCI. In 2 dogs calcium-disodium EDTA, which has no effect on the serum calcium, changed neither the $P_{12.5}$ index nor dp/dt Max. until infused at a rate which would have caused myocardial arrest with trisodium EDTA, indicating that the effects of the latter were due almost entirely to the decreased serum calcium rather than to a nonspecific effect of the EDTA itself.

Circulatory function during anesthesia is characterized by a high level of sympathetic nervous activity. In order to evaluate the possibility that the diminution in contractile strength by hypocalcemia might have been due in part to blockage of the action of adrenalin or noradrenalin, these substances were infused intravenously in 3 dogs at a rate of 7 mg. per minute for 20 minutes. The increases in the $P_{12.5}$ index and dp/dt (Max.) induced by infusion of the amines were the same at a serum calcium level of 6.0 mg. per cent as at the normal level of 10.0 mg. per cent.

CHANGES IN SERUM Na (TABLE II). The pressure function curve was not changed significantly by *hyponatremia* in 8 experiments at levels of 116 to 130 mEq. per liter or by *hypernatremia* in 10 experiments at levels of 163 to 218 mEq. per liter. The cardiac output, heart rate, and dp/dt Max. were increased by the infusion of 5 to 10 per cent of NaCl, but not by the infusion of hypotonic NaCl or hypertonic mannitol solutions which induced changes in the blood hematocrit (averaging 5.0 units) smaller than those induced by the NaCl solutions (averaging 12.0 units).

CHANGES IN SERUM K (FIGS. 4, 5, TABLE II). Only minimal *hypokalemia* (to 2.1 and 2.5 mEq. per liter) was induced in the 2 experiments using artificial dialysis. Minimal effects were observed on the parameters listed in Table II. The ineffectiveness of the Kolff coil in producing hypokalemia acutely in the intact dog interdicted fur-

ther experiments for this purpose in the present study. *Hyperkalemia* (8.4 to 11.5 mEq per liter) produced by the infusion of isotonic KCl was carried in each of 12 dogs to the point of complete atrioventricular block, atrial standstill, and idioventricular or nodal rhythm and was maintained for as long as 3 hours. The arrhythmias usually occurred at a serum [K] of about 9 or 10 mEq per liter. The heart rate fell and the arterial blood pressure and ventricular stroke work rose (Table II), but no significant persistent change in ventricular contractile strength or dp/dt Max was observed (Fig. 4 and Table II), even in the presence of marked electrocardiographic abnormality. Further elevation of the serum K in each experiment caused temporary or permanent cardiac arrest. In 3 experiments the infusion of KCl transiently increased the $P_{12.5}$ index and dp/dt Max for 10 to 15 minutes, possibly because of epinephrine discharge.[16] These brief effects have been excluded in deriving the data of Table II. After the administration of DCI in 4 experiments no effects suggestive of epinephrine discharge were observed during subsequent infusion of potassium. Changes in heart rate, blood pressure, and stroke work were similar to those observed without DCI. The $P_{12.5}$ index gradually fell to the control values observed before the administration of DCI (Fig. 5), possibly

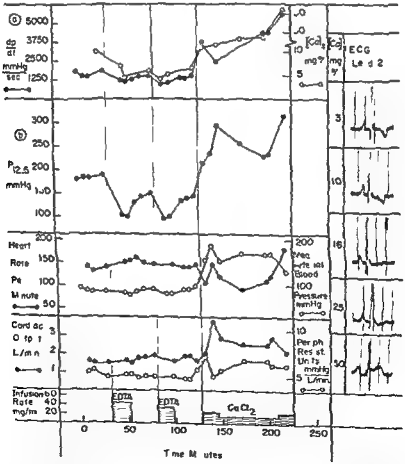

Fig. 3. Correlation of various ventricular functions with serum calcium concentrations during infusions of EDTA and $CaCl_2$. dp/dt Max (panel *a*) is the maximum rate of rise in the left ventricular pressure pulse. $P_{12.5}$ (panel *b*) is an index obtained from the pressure function curve. It is the peak ventricular systolic pressure at an end-diastolic pressure of 12.5 mm. Hg during graded aortic obstruction.

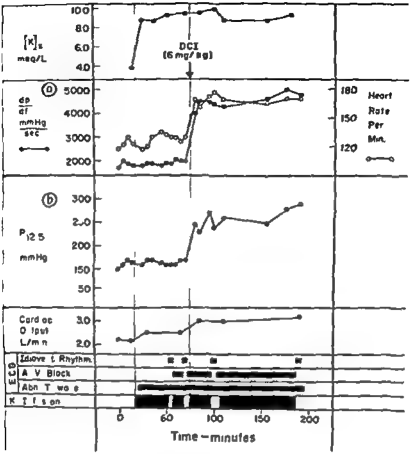

Fig 4 Changes in left ventricular functions and the effects of DCI (dichloroisoproterenol) during hyperkalemia Abbreviations as in Fig 3

because of a waning action of the drug The possibility that hyperkalemia might have blocked the action of DCI was discounted by the observation that the effects of DCI were evident when the drug was administered *during* hyperkalemia (Fig 4)

CHANGES IN BLOOD pH (FIGS 6 7 TABLE II) The infusion of $NaHCO_3$ (4 6 mEq per kilogram) in 3 dogs induced hypernatremia and mild *alkalosis* (to pH 7 57) The cardiac output was transiently augmented but returned to control values within 30 minutes Stroke work and dp/dt Max were increased but the pressure function curve was unchanged (Table II) The infusion of HCl (4 6 mEq per kilogram) induced *acidosis* of variable degree depending on the degree of respiratory compensation (the total serum bicarbonate was uniformly reduced to about 12 mEq per liter) In 4 dogs the reduction in the blood pH to the range of 7 02 to 7 23 units had no effect on the $P_{12.5}$ index or dp/dt Max The possibility that an effect of this degree of acidosis on ventricular function was being counteracted by epinephrine discharge[18] was discounted by 4 experiments in which acidosis in the range of 6 97 to 7 11 units also did not affect the $P_{12.5}$ index or dp/dt Max after epinephrine blockade by DCI (Table II) although heart rate was reduced and stroke work and blood pressure were increased (Table II) However when the dosage of HCl was increased so as to lower the serum pH in 5 dogs to the range of 6 80 to 6 92 units marked circulatory and cardiac effects were observed whether DCI was used or not (Figs 6 and 7) The ventricular function curve was depressed EDP was increased and dp/dt Max $\frac{\text{dp/dt Max}}{\text{EDP}}$ and heart rate were reduced although cardiac output was not significantly changed (Table II)

Discussion

In the present experiments, a direct relationship was observed between the serum calcium concentration and both left ventricular contractile strength (as measured by the pressure function curve) and the maximum rate of rise in ventricular pressure (dp/dt Max) It is unlikely that the effects of hypercalcemia were due to a discharge of epinephrine since they were also observed after the administration of DCI which blocks the cardiac effects of epinephrine and norepinephrine[15,16] The changes in heart rate induced by the infusions of $CaCl_2$ and EDTA were too small (see Fig 1) to have caused the large changes in the $P_{12.5}$ index and in dp/dt Max observed during hypocalcemia and hypercalcemia The alterations in ventricular end-diastolic and arterial blood pressures were opposite to those which would have explained the concomitant changes in dp/dt Max and would not have affected the pressure function curve at all (see introductory section) Therefore it is probable that hypocalcemia and hypercalcemia influenced ventricular function by direct action on the myocardium which indicates the applicability of previous data from isolated hearts[1,2,3] or muscle strips[4,5] to ventricular function in the intact animal In addition the present experiments with hypocalcemia illustrated the remarkable capacity of the intact circulation to maintain the cardiac output in the face of marked impairment of ventricular contractile strength Ventricular ejection was preserved by the operation of the Starling mechanism as judged by the simultaneous increase in left ventricular end-diastolic pressure and the fall in aortic blood pressure and heart rate which implied a lack of reflex sympathetic nervous discharge

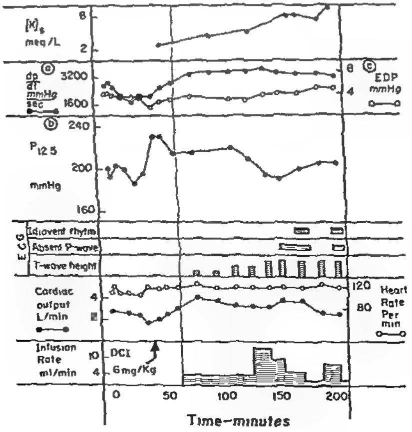

Fig 5 Changes in several ventricular functions during severe hyperkalemia induced by the infusion of KCl (150 mEq per liter) after the administration of DCI Abbreviations as in Fig 3

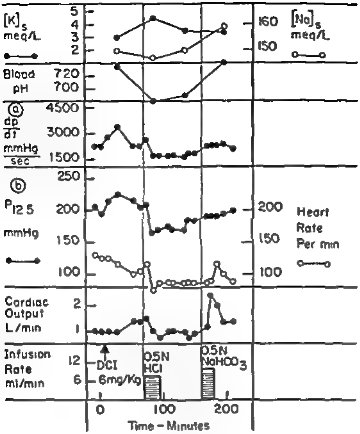

Fig. 6 Changes in several ventricular functions during DCI blockade and severe acidosis induced by the infusion of HCl. Abbreviations (a) and (b) as in Fig. 3.

In the present experiments *hypokalemia* (to 2.1 mEq per liter) and *hyperkalemia* to the point of diminished myocardial excitability, impaired electrical conduction, and imminent cardiac arrest (at 10.0 to 11.5 mEq per liter) caused no measureable change in either the pressure function curve or in dp/dt Max. These results differed from those expected on the basis of studies of isolated hearts or muscle strips[4,6] in which contractile force declined when the potassium concentration of the nutrient medium was changed above or below the normal value. On the other hand, the results were consistent with the recent observation that the isometric contractile force of isolated cat papillary muscle was unchanged by graded 5 minute elevations of the concentration of potassium in the bathing fluid up to the point of inexcitability.[8] In addition, the present data indicate preservation of ventricular contractile function despite persistence of hyperkalemia for as long as 3 hours. In view of the evidence which has been presented[11] that injection of potassium salts stimulate the secretion of epinephrine, it was possible that the secretion of epinephrine in the present experiments might have counteracted an otherwise depressant effect of hyperkalemia on ventricular function. However, by avoiding bolus injections and by recording (Table II) only the data obtained after the first 30 minutes after elevation of the serum [K], this possibility was minimized. The experiments using DCI prior to injection of KCl also supported the view that adrenalin discharge was not responsible for the preservation of ventricular contractile strength during severe hyperkalemia.

Acidosis (to pH 7.0) induced by an excess of carbon dioxide causes heart failure in the heart lung preparation and

reduces the contractile amplitude of the isolated mammalian (but not the amphibian) cardiac ventricle.[17-20] Acidosis of the same degree in the intact animal, on the other hand, is not attended by heart failure,[19-21] although transient reduction in right ventricular contractile force as measured by a strain gauge arch has been reported.[20, 4] The present experiments provided further evidence of the tolerance of the intact animal to acidosis. No heart failure or impairment of left ventricular contractile strength as estimated by the pressure function curve was observed during HCl induced acidosis to a blood pH as low as 7.0 units. These results did not appear to be related to compensatory effects of catecholamines since they were also observed after catechol blockade by DCI, the sympathomimetic effect of which was maximal before the acidifying infusion. The limit of cardiac tolerance to acidosis was reached at pH 7.0. When the blood pH was below this value, persistent impairment of left ventricular function was evident and end-diastolic pressure rose while heart rate declined (Table II). The bradycardia was not sufficiently marked to explain the changes in ventricular function observed (Fig. 1). It was of interest also, that although it has been reported that the cardiac response to epinephrine and norepinephrine may be eliminated by a reduction in the blood pH below 7.0 units,[4] the pressure function curve and dp/dt Max were sharply augmented by DCI which was administered during severe acidosis in several of the present experiments (Fig. 7). The usefulness of a sympathomimetic drug such as DCI therefore to support the heart and circulation during severe acidosis (pH below 7.0 units) was clearly documented.

A low extracellular (Na) has been shown to augment the contraction of the isolated frog or rat ventricular muscle[1,3,7] although not of the isolated cat papillary muscle.[5,6] A high extracellular [Na] and hyperos

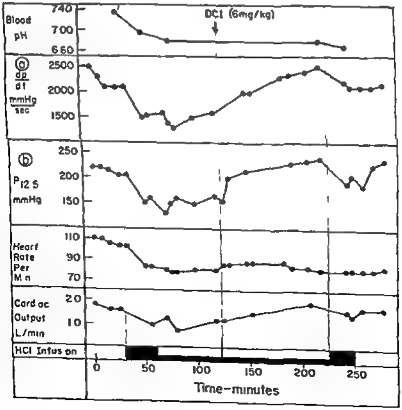

Fig. 7. Changes in left ventricular functions and the effects of DCI during severe acidosis induced by the infusion of HCl. Abbreviations as in Fig. 3.

molarity[4] have been reported to diminish the contractile force of the isolated frog heart and cat papillary muscle, respectively. In the present experiments changes in the serum [Na] were without significant effect on the left ventricular pressure function curve, although hypernatremia augmented cardiac output, heart rate, and dp/dt Max., in accordance with previous observations of the effect of hypertonic solutions on the circulation.[16,27] These apparently discrepant observations relating ventricular function to extracellular [Na] may be resolved by considering the magnitude of the change in [Na] induced in each study. A significant change in ventricular function might be anticipated at a serum osmolarity of more than about 480 mosmol per liter[4] (equivalent to a serum [Na] of about 225 mEq. per liter) or at a serum [Na] of less than 117 mEq. per liter.[7] Changes in the extracellular [Na] in the previous experiments with isolated cat papillary muscles[4,6] and in the present study were at or within the limits of these values and therefore not clearly in the ranges in which changes in ventricular function could be expected.

In so far as these experiments in anesthetized dogs are applicable to human subjects, the results are pertinent to several aspects of the management of heart failure in man. A diminution in left ventricular contractile strength which would be of no serious consequence to the normal subject might be critical for the patient with heart disease who was already functioning at the limit of his cardiovascular reserve. *Hypocalcemia* is one of the two electrolyte abnormalities which, according to the present study, would be of chief concern in this regard. In addition to various forms of chronic hypocalcemia, the acute disorder induced by the administration of Na_2EDTA would be of particular importance. Exaggeration of the manifestations of left ventricular failure might be anticipated when this substance is used to treat toxic arrhythmias due to digitalis or quinidine.[28] *Acidosis* was the other electrolyte abnormality which would be expected, on the basis of the present study, to impair left ventricular contractile function, although only if the serum pH were below 7.0 units. The present experiments suggest that cardiac function could be quickly improved during such severe acidosis by the use of a sympathomimetic drug such as isoproterenol (a close congener of DCI), pending correction of the acidosis by other methods.

Summary

Left ventricular function in the intact anesthetized dog was evaluated by measurements of the ventricular response to a pressure load (the pressure function curve), the maximum rate of rise in intraventricular pressure (dp/dt Max.), end-diastolic pressure, and cardiac output.

Observations were made of the effects on these measurements of changes in heart rate and in various serum electrolyte concentrations or in blood pH induced by infusions of NaCl, $NaHCO_3$, HCl, mannitol, EDTA, and $CaCl_2$ or by dialysis with an artificial kidney. Sympathomimetic effects of injected solutes were evaluated by blockade with DCI (dichloroisoproterenol).

Bradycardia at rates below 80 beats per minute reduced dp/dt Max. and depressed the pressure function curve. However, changes in rate in the range pertinent to the electrolyte experiments (between 80 and 160 beats per minute) had only minimal effect on the pressure function curve. The only electrolyte disturbances which altered the pressure function curve were hypercalcemia and hypocalcemia and acidosis to a serum pH of less than 7.0 units. Hyperkalemia to the point of cardiac arrest had no effect on the curve.

These results extend the previous brief observations made in isolated heart or muscle preparations to periods of several hours in the intact animal. They have a bearing on several clinical problems in the management of heart failure in human subjects.

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Experimental comparison of "parallel grid leads" with simple bipolar, and the SVEC-III, Frank, and McFee-Parungao systems I Sagittal leads

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Corrected lead systems especially that of Frank[1] are increasingly used in published clinical studies although experimental evidence concerning their performance other than that supplied by the originators of the leads remains scarce A compromise between excellence and economy especially in electrode numbers is evident in the original design of these leads as well as in their clinical application The three corrected systems of Frank[1] Schmitt and Simonson and McFee and Parungao[3] included in the present study were carefully designed as an optimum compromise between many conflicting factors such as soundness of theoretical basis accuracy vulnerability to dipole location ease and speed of application[1] as the best orthogonal leads which can be made consistent with reasonable simplicity[2] and as a carefully drawn compromise between the simultaneous need to maximize accuracy and minimize complexity[3] The suggestion that more complex leads are more accurate but less practical is implied in these statements It is explicit in McFee and Parungao's use of ideal leads composed of many electrodes effectively covering the entire body in checking the accuracy of their new axial lead[3]

Since convincing evidence of the superiority of the Frank or of any other corrected lead system does not emerge from published comparison[4-8] the increasing use of the Frank system seems to be due not to the excellence but to the relative simplicity of the system The magnitude of the conflict between accuracy and practicability is reduced by using no paste electrodes since a multielectrode bank of balsa lithium no paste electrodes is not more laborious to apply than standard leads using paste[9-11] A final selection of a lead system for clinical use thus seems to be premature without first considering the multielectrode leads which are made possible by no paste methods

The present experimental comparison of leads was undertaken to supply quantitative data on which to base a choice of an orthogonal lead system for clinical use The sagittal leads are treated in this communication the transverse and vertical leads in a future one[8] The accuracy of grid leads in measuring the total outward dipole moment of the heart using the equation

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$$M = AV/\rho$$

derived by Barber and Fischmann [9,10] is now tested experimentally in the homogeneous torso model

Mathematics and the clinician The future of the application of electrocardiographic theory is in the hands of the clinician and therefore dependent on physicist physician communication It was said that mathematical methods tend to induce a strong emotional reaction in nonmathematical minds because it is exasperating to find our conclusions questioned by someone who could not have made the observations himself [1] and that mathematical elaborations are abhorrent to medical practitioners mainly because they reveal the insecurity of the conclusions we like to make [11] Although it is likely that physicians with these attitudes do exist there are at least four other large groups those without mathematical ability those who acquire a mathematical method when its usefulness is proved those with a knowledge of mathematics and finally some who quite legitimately hold the view that physicians should resist spending time on mathematics and other fields which now overlap with medicine lest they shall end up poor physicians When an electrocardiographic method begins to mature toward clinical use its authors writing for such an inhomogeneous public have a choice of possibilities ranging from continued noncommunication to nonmathematical presentation of mathematical matter A compromise accepting the onus of intelligibility which after all is on the authors is attempted in this paper Mathematical matter is confined to the section on theory

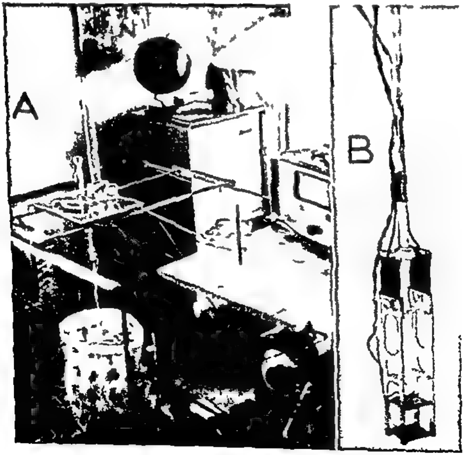

Fig 1 A Torso model three-directional carrier of current source and plotting table B Current source its top plate-pair delivers x-directed or if rotated 90 degrees z-directed current The source can be moved up so that the lower plate pair then delivers y-directed current in a position previously occupied by the x z pair

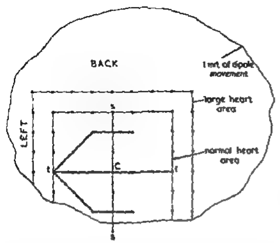

Fig 2 Transverse torso cut at the level of C the approximate center of gravity of the ventricles Normal heart area defined by transverse and sagittal diameters of the heart shadow tt and ss Large heart area obtained by 2 cm extension left right and backward The 59 points explored at 2 cm intervals at this level are shown In addition the torso is similarly explored at levels 6 cm headward and footward of point C a total of 177 points for each lead A reduced heart consists of 13 points within the approximate septum and ventricular walls (*heavy line*) at one level only

and can be bypassed without loss of context The rest is mainly nonmathematical containing the single equation quoted before

Experimental lead testing method

The current source shown in Fig 1 designed to deliver x y and z directed current is immersed in a previously described[14] fiber glass torso model filled with tap water Brass screws in the wall of the model are arranged to correspond to the leads investigated The source is excited by a 70 c p s alternating current from a balanced output oscillator Lead voltages are measured by a vacuum tube voltmeter (error ± 2½ per cent) A Philips PR9500 conductivity bridge measures the resistance of the current source and of the resistivity of the torso

A manually operated three way mechanism mounted above the torso moves the current source within the model An arm transmits the positions of the current source to maps (Fig 2) Each map shows the following items determined from frontal and sagittal teleradiograms of the patient on whom the torso was moulded (1) Point C corresponding to the approximate center of gravity of the ventricles (2) A normal heart area its width and depth determined by the radiologic transverse and sagittal diameters of the heart

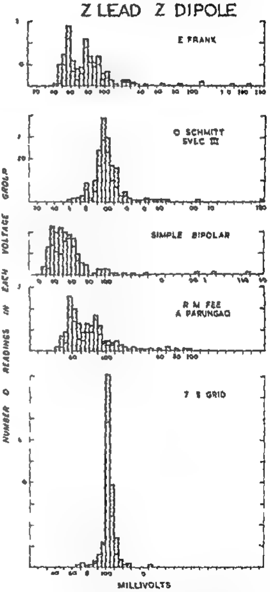

Fig 3 Sensitivity to change in dipole position as a measure of nonuniformity The z directed current source at the center of gravity of the ventricles is set to give a voltage of 100 mv in the sagittal lead under study The source is then moved to 177 points within the large heart area The distribution of the corresponding 177 sagittal lead voltage readings within the normal (*unshaded*) and the large (*unshaded plus shaded*) heart areas is shown An ideally uniform lead would show 177 readings of a single modal mv value

at level C (3) A large heart area obtained by 2 cm extension of the normal area left right and backward (4) A reduced heart consisting of 13 points within the approximate cardiac septum and ventricular walls The maps also show (5) 59 points defined by a 2 cm² network and (6) the limit of possible current source movement This limit does not coincide with the wall of the model because of restriction by the waist of the model The anterior border of the heart area is determined by this limit

The torso is explored with the current source moving at three levels at the level of C the approximate center of gravity of the ventricles and at levels 6 cm headward and footward respectively of C At each of the three levels the source is moved to 59 points as in Fig 2 a total of 177 points for each lead explored The lead voltage is read with current x y and z-directed respectively at each of these points 531 readings for each lead from the large heart Of these readings data from 120 and 13 points respectively are taken to represent the normal and reduced hearts (Fig 2)

The following five leads are investigated by this method the sagittal leads of the systems of Frank[1] Schmitt Simonson (SVEC III) and McFee Parungao[2] a simple bipolar sagittal lead consisting of a precordial electrode over the approximate center of gravity of the ventricles and another electrode on the back[13,14] and the 7 by 5 parallel grid lead[9,10]

Reference current and voltage At the onset of each experiment the current source is at the center of gravity of the ventricles C within the model The source is rotated to be codirectional with the

Table I Nonuniformity of five sagittal leads in terms of variation in lead voltage caused by changes in the position of a z directed current source within the homogeneous torso (means and S D in mv)

Lead	Arithmetic scale		Logarithmic scale		Significance of logarithmic S D		
	Mean	S D	Mean	S D	$p = 0.001$	$p = 0.01$	$p = 0.05$
A Large heart (177 voltage readings)							
Grid	103 4	8 5	2 013	0 037	a	a	a
Schmitt	102 3	23 5	2 001	0 094	b	b	b
McFee	80 9	29 1	1 884	0 137	c	c	c
Frank	80 5	33 6	1 879	0 144	c	c	c
Bipolar	57 8	31 2	1 724	0 190	d	d	d
B Normal heart (120 voltage readings)							
Grid	101 6	6 9	2 006	0 033	a	a	a
Schmitt	99 5	17 4	1 992	0 075	b	b	b
McFee	86 6	31 2	1 914	0 138	c	c	c
Frank	83 7	36 0	1 895	0 144	c	c	cd
Bipolar	64 6	35 2	1 771	0 169	c	c	d
C Reduced heart (13 voltage readings)							
Grid	99 9	3 4	2 000	0 015	a	a	a
Schmitt	103 [illegible]	15 6	2 008	0 068	b	b	b
McFee	110 3	22 6	2 033	0 083	b	b	b
Frank	124 2	49 6	2 066	0 160	b	bc	c
Bipolar	114 9	71 3	1 998	0 225	b	c	c

Methods which have a letter in common are not significantly different at the stated significance level whereas any two methods which do not have a letter in common do differ significantly For definitions of large normal and reduced hearts, see Fig 2 Leads are grouped in order of increasing scatter of lead voltage values, [illegible] increasing nonuniformity The variance of the standard deviation in normal samples is $S^2/2n$ where S is the estimate of the standard deviation of the normal distribution For a log normal parent distribution it is approximately $S^2/2n(1+k)$ where k [illegible] of the standard deviation (on the logarithmic scale) of the parent distribution such as those observed the correction is small, 0.3 at the most but it has been incorporated so tests are at least conservative in the sense of not wrongly [illegible] significance

lead under study and excited to cause a 100 mV reference voltage in the lead. The source current remains constant throughout each experiment so that when the source is moved to other parts of the torso interior or when its direction is changed the resulting lead voltages are read directly as percentages of the reference.

Criteria of lead accuracy

Except in experimental "tuned"[11] and null[17] leads present electrocardiographic methods including unipolar leads record voltages caused by the added effects of electromotive forces in all simultaneously activated cardiac areas. Three criteria of the accuracy of this type of lead—two of which are widely accepted, the third here introduced—are used in the evaluation of the present experiments. (1) *Uniformity.* An ideally uniform lead is defined as giving a constant voltage response to a given force irrespective of where within the heart the force originates. Conventional electrocardiographic and most vectorcardiographic leads record from unequally weighted area contributions since their response depends not only on the force but also on its position within the heart.[18] (2) *Orthogonality.* The voltage in an ideally orthogonal lead is maximal when the force is codirectional with the lead and is zero when the force is perpendicular. Orthogonality is one criterion of the ability of a lead to isolate the measured quantity without contamination by other effects. Most electrocardiographic and vectorcardiographic leads measure unknown mixtures of x, y, and z contributions. (3) *Ability to measure quantitatively the total outward dipole moment of the heart.* Gabor and Nelson[15] achieved this by voltage integration over the body surface but because of its laboriousness they did not regard this as a clinical procedure. Barber and Fischmann[9,10] described a clinically practical method that is used in the present work.

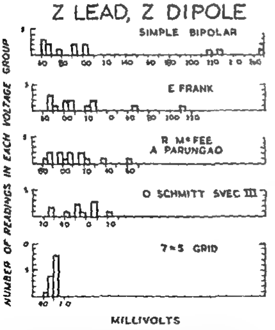

Fig. 4. Sensitivity to change in dipole position as a measure of nonuniformity. The distribution of lead voltages with the z-directed current source in only 13 positions within the approximate septum and ventricular walls ("reduced" heart). The source placed at the center of gravity of the ventricles was set to give a voltage of 100 mv. in the sagittal leads under study. An ideally uniform lead would show 13 readings of a single modal mv. value.

With the present experimental method an ideally uniform sagittal lead would give 177 voltage measurements, each identical with the reference value when the z-directed dipole is in 177 positions within the model. An ideal orthogonal lead would yield two sets of 177 zero voltages when the source is x or y directed, respectively, in the 177 positions. This degree of accuracy is not approached in any of the leads studied. Therefore the evaluation is performed in negative terms by comparing nonuniformity and nonorthogonality.

Parallel grid leads

The sagittal grid lead tested in the present experiments derives from the sagittal lead suggested by Reynolds and associates.[19] The field uniformity of the latter improves and becomes independent of torso shape if the spacing of the units of each grid, as projected on the frontal plane, is kept uniform regardless of the slope of the torso surface.[10] It was also shown[10] that if the field is uniform not only in the heart but also throughout the torso, then an orthogonal system formed by leads of this type will perform the surface voltage integration suggested by Gabor and Nelson[15] for the determination of the resultant

dipole of the heart. With the use of balsa lithium no-paste electrodes[11] integration with parallel grids in clinically practical—multielectrode platforms take no longer to apply than single metal electrodes and paste. Thus the 7 by 5 grid lead used in the present experiments differs from that suggested by Reynolds and associates[13] in the employment of grids which are large enough to cover most of the chest, abdomen, and back, and which are symmetrically placed on the torso and require no paste electrodes. Also the electrodes of the anterior grid are platform mounted as previously described[19] to retain uniform projected spacing. The lead differs from the one we have previously described in having 35 electrodes uniformly spaced at 6.5 cm. each back and front, higher individual resistor values of 100,000 ohms, and a single Perspex sheet platform.

The performance of a parallel grid lead is elucidated by considering an imaginary box-shaped torso model.[8, 9] The opposing anterior and posterior surfaces of the box are the two electrodes of the sagittal lead. If a uniform amount of current is made to enter all points of the dorsal surface and leave through the anterior surface, parallel and equidistant z-directed current flow lines exist throughout the model, or in terms of the McFee-Johnston[9] lead field concept, the sagittal lead has a uniform field. Let a current I flow through a z-directed pair of small metal plates immersed anywhere in the box and having a

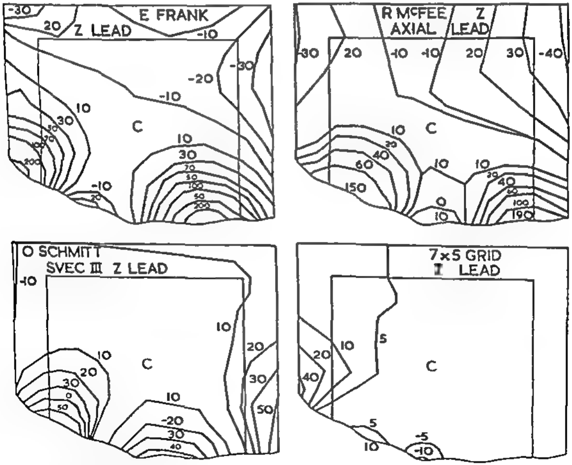

Fig. 5. Sensitivity of sagittal leads to a change in dipole position as a measure of lead nonuniformity. The strength of the z-directed current source is adjusted to yield a lead voltage of 100 mv. while the source is at point C, the approximate center of gravity of the ventricles. Per cent changes in lead voltage from this value while the z-directed dipole is moved within a single transverse torso level are shown.

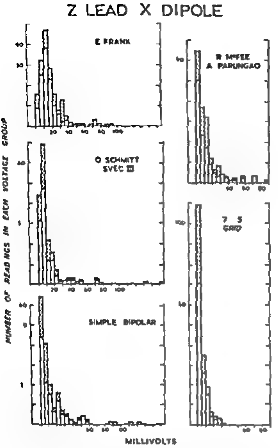

Fig. 6. Sensitivity of sagittal leads to x directed current as a measure of nonorthogonality, in mv per cent of the lead voltage obtained when the z directed source is at the center of gravity of the ventricles. Normal (*unshaded*) and large (*shaded plus unshaded*) heart areas. In an ideally orthogonal lead all values are zero.

short interplate distance d. The product I d is the dipole moment M of this current source. A simple relationship exists between M and the sagittal lead voltage V, which is the difference in potentials between the posterior and anterior surfaces of the box. This relationship is given by the equation

$$M = A \cdot V / \rho \qquad (1)$$

where A, the area of the posterior or anterior box surface, and ρ, the resistivity of the torso, are known. Thus if the lead voltage V is measured, the dipole moment of the source M is also known. Similar equations exist for transversely and vertically directed leads.

Equation (1) holds for all positions of the current source within the box. It follows that this lead is ideally uniform in its response. Since it shows maximal response to z-directed and zero response to x-directed and y directed current sources, it is also ideally orthogonal, as can be shown.

A lead with approximately equivalent performance can be obtained if the opposing faces of the box are replaced by a sufficiently numerous set of electrodes and each electrode of a set is connected through a large equal resistor to the lead wire.[9,10,20] In the parallel grid lead system the method is extended by virtually enclosing the torso in the space defined by three pairs of flat surfaces, each surface carrying a suitable multielectrode set.[9,10] In practice the sets corresponding to the transverse and vertical leads, respectively, are represented by simplified equivalents.

Results

Determination of dipole moment with the parallel grid lead. The dipole moment of the z directed current source within the torso model is determined in two ways: (1) directly from the known potential difference, resistance, and distance between the horizontal plate pair of the source and (2) with the sagittal grid lead using Equation (1). In the torso experiment A is the area enclosed by the electrodes of the grid extended by half an electrode interspace in four directions, V is the lead voltage, and ρ is the resistivity of the tank water. The dipole moment M determined with the lead differs from directly measured M by a typical margin of ±5 per cent.

Nonuniformity of leads in terms of variation in voltage caused by changes in dipole position. Figs. 3 and 4 show frequency distributions of individual voltage values in samples of 177, 120, and 13 readings from the large, normal, and reduced heart areas, respectively. Between leads differences are sufficiently marked to allow separation into three groups by inspection of the graphs. The grid shows the least scatter. The sagittal SVEC III lead is intermediate between the grid and the least uniform group which consists of the other 3 leads.

Maps of per cent change in lead voltage

when the current source is moved within the transverse torso plane are also used in judging nonuniformity (Fig 5) Here again SVEC III is intermediate between the grid and the group formed by the least uniform Frank and McFee Parungao leads

As quantitative indicators of nonuniformity standard deviations seem to be acceptable in the approximately Gaussian distributions shown by the grid and SVEC III leads but not in the more asymmetrical distributions from the others However on a logarithmic scale of millivolts all five leads show a near Gaussian distribution Table I shows the arithmetic and logarithmic standard deviations for each lead The division into a most uniform intermediate and least uniform group

Fig 7 Sensitivity of sagittal leads to y-directed current as a measure of nonorthogonality in mv per cent of the lead voltage obtained when the current source is z directed at the center of gravity of the ventricles In an ideally orthogonal lead all values are zero

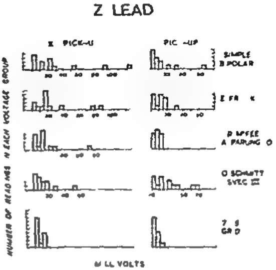

Fig 8 Sensitivity of sagittal leads to x and y directed current in mv per cent of the lead voltage obtained when the current source is z directed at the center of gravity of the ventricles The heart is reduced to consist of only 13 points within the approximate septum and ventricular walls shown in Fig 2 In an ideally orthogonal lead all values are zero

is again evident As judged by both the arithmetic and logarithmic standard deviations SVEC III shows approximately three times greater scatter than the grid If the logarithmic standard deviations are used as the criterion highly significant differences appear between SVEC III and the grid on the one hand and SVEC III and the least accurate group on the other The advantage of the SVEC III lead over the latter group is less than the advantage of the grid over SVEC III The nonuniformity of the least accurate group is approximately twice greater than that of SVEC III The simple bipolar lead shows the greatest scatter of any lead in all three heart sizes but in the normal and reduced hearts the difference between it and the Frank and McFee Parungao leads is not significant at the 0 01 level This difference is significant in the large heart ($p = 0.001$)

Nonorthogonality of sagittal leads in terms of x and y pickup Figs 6 8 show the frequency distributions of sagittal lead voltages when the current source is x and y directed respectively within the cardiac areas of the model Table II gives the means of these ... Since y

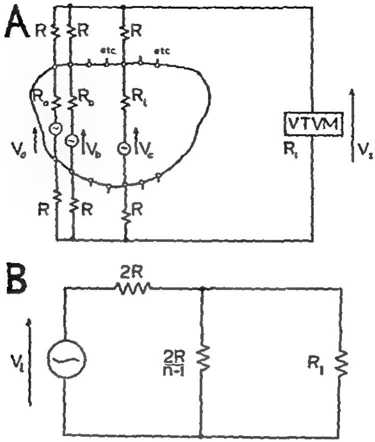

Fig. 9. See text.

ever the distribution of individual values the distribution of the means tends to be Gaussian in large samples but not necessarily so in small ones, the t test is employed in the large and normal but not in the reduced heart where only 13 measurements are available from each lead. All x and y pickup readings from an ideally orthogonal lead would be zero. In Figs. 6-8 the grid shows the least deviation from zero. The four other leads do not seem to differ greatly and orthogonality grading by inspection alone would be hazardous. Statistical grading is attempted in Table II and the leads are shown in order of decreasing orthogonality. In each of the six sets in Table II the grid with less than 6 per cent mean pickup is the most orthogonal. The sagittal lead of Frank is with equal consistency at the opposite end of the scale and exceeds all leads including the simple bipolar in nonorthogonality in the large and normal hearts. The difference between the grid and other leads is significant ($p = 0.001$). Of the remaining corrected leads none shows a consistent advantage over the other or over the bipolar lead.

Parallel grid lead theory

The basic formula for determining the component dipole moments assuming a uniform field electrode system is derived by Barber and Fischmann.[9,10] Thus for the z component

$$M = \frac{A_x}{\rho} \sum_{i=1}^{n} V_i \qquad (2)$$

where V_i is the potential difference between the i^{th} pair of electrodes, $A = nA_i$ is the total effective projected area of the sagittal electrode set, n is the number of pairs of electrodes, and ρ is the uniform isotropic resistivity of the conducting medium. Similar forms of Equation (2) exist for the other two orthogonal dipole components.

A practical rapid way of measuring V_t which avoids the tedious individual measurement of each voltage difference and their summation is to use an isolating resistor bank connected to all the n pairs of electrodes. Fig. 9,A shows part of the circuit, where R_i is the Thévenin source resistance between the i^{th} pair of electrodes and R_1 is the VTVM input resistance.

The isolating resistors R serve three important purposes provided that $2R \gg R_s$, where R_s is the largest value of the source resistances. (1) They limit the circuit loading on the electrode set so that the open circuit distribution of potential in the torso is not altered significantly by external currents through the resistor bank and external circuitry. (2) They allow simplification of the formula (derived below) relating VTVM reading V_m to the quantity to be measured ΣV. (3) They simplify measurement by eliminating the need for knowledge of the actual values of R, R_1, [illegible] R.

Application of the superposition theorem to the measuring circuit (Fig. 9,A) leads to the simple equivalent circuit for the i^{th} generator as in Fig. 9,B.

Each generator voltage suffers the same attenuation ratio of the above network, i.e., $R_1/2R + nR_1$ (which is easily derived), so that by using superposition again V_m is given by

$$V_m = \frac{R_1}{2R + nR_1}(V_1 + V_2 + \dots) = \frac{R_1}{2R + nR_1}\Sigma V$$

or

$$\Sigma V = \frac{2R + nR_1}{R_1} V_m \qquad (3)$$

By making $nR_1 \gg 2R$, further simplification occurs. Thus, for the tank model

Table II. Nonorthogonality of five sagittal leads in terms of mean "pickup" voltages (mv.) when the current source within the torso model is x or y directed (in an ideally orthogonal lead all means are zero)

Pickup from x directed source					*Pickup from y directed source*				
Lead	*Mean*	*p = 0.001*	*p = 0.01*	*p = 0.05*	*Lead*	*Mean*	*p = 0.001*	*p = 0.01*	*p = 0.05*
A. Large heart (177 voltage readings)									
Grid	5.7	a	a	a	Grid	4.3	a	a	a
McFee	12.1	b	b	b	McFee	17.2	b	b	b
Schmitt	13.1	bc	b	b	Bipolar	17.4	bc	b	b
Bipolar	13.5	bc	bc	b	Schmitt	19.9	bc	bc	bc
Frank	18.3	c	c	c	Frank	23.4	c	c	c
B. Normal heart (120 voltage readings)									
Grid	5.7	a	a	a	Grid	4.4	a	a	a
McFee	11.7	b	b	b	McFee	17.4	bc	b	b
Schmitt	12.9	b	b	bc	Schmitt	19.6	bc	bc	bc
Bipolar	15.4	b	b	bc	Bipolar	20.1	bc	bc	bc
Frank	15.9	b	b	c	Frank	24.4	c	c	c
C. Reduced heart (13 voltage readings)									
Grid	5.[illegible]				Grid	4.3			
Schmitt	12.0				McFee	7.2			
McFee	14.5				Bipolar	13.2			
Frank	20.0				Frank	14.5			
Bipolar	30.2				Schmitt	29.2			

Leads [illegible] grouped in order [illegible] increasing mean s[illegible] e [illegible] ncre[illegible] g [illegible] orth g[illegible] l ty. Method wh[illegible] h h[illegible] [illegible] mm n a[illegible] not significantly different wb reas[illegible] y tw[illegible] method [illegible] [illegible] large, normal, [illegible] d[illegible] ted ced hearts see Fig. 2.

typical values are

$$R_j \cong 6 \text{ k}\Omega \quad R = 100 \text{ k}\Omega$$
$$R_1 = 4 \text{ M}\Omega \quad n = 30$$

so that Equation (3) becomes to a close approximation simply

$$\Sigma V = nI \tag{4}$$

(This rapid method of measurement was compared experimentally with individual V measurement and summation The results agreed to within 3 per cent)

Substituting Equation (4) back into Equation (2) yields the final form for the dipole moment relation

$$M = \frac{I A}{\rho} \tag{1}$$

The validity of Equation (1) was checked by means of the homogeneous torso model as described earlier in this paper

A frequency of 70 c p s was chosen for the present work Above about 200 c p s errors were observed For instance the signal picl up by the z lead was about 30 decibels down when the dipole was oriented in the x or y direction and was constant for frequencies from 15 to 150 c p s but isolation diminished rapidly as the quency was raised This effect is prob y due to capacitive effects from source to ground However the use of low fre quencies is not precluded by polarization Polarization effects were not observed even at frequencies as low as 15 c p s when the resistivity of water was measured in the range of 15 c p s to 3 kc/s and found to vary less than 1 per cent The power frequency 50 c p s was not used in order to avoid hum errors

Summary

A performance comparison of the following five leads is made in the homogeneous torso model The sagittal leads of the Frank Schmitt Simonson SVEC III and McFee Parungao lead systems a simple bipolar lead consisting of a precordial and dorsal electrode and a 7 by 5 parallel grid sagittal lead The criteria of uniformity orthogonality and ability to measure the total outward dipole moment of the heart are used in judging lead quality

A point of reference corresponding to the approximate center of gravity of the ventricles and concentric 'large ' normal and reduced heart areas are defined within the model and on maps placed on a drawing board near the model A current source able to deliver x y and z directed current is three directionally movable within the model and its position is transmitted to the drawing board by means of a rigid arm The source z directed at the point of reference within the torso is excited to deliver current which is sufficient to cause a 100 mv reference voltage in the lead under study Lead voltages obtained when the source is x y or z directed at 177 points within the cardiac area of the torso are then read directly as percentages of the reference voltage In an ideally uniform lead 177 readings of 100 mV are obtained when the source is z directed In an ideally orthogonal lead two sets of 177 zero readings are obtained when the source is x and y directed respectively

1 By inspection alone of graphs which show the frequency distribution of individual voltage readings around these standards of ideal accuracy and of torso maps which show lines of percentage deviation from the reference voltage leads are grouped as follows (i) the least accurate group containing the Frank McFee Parungao and bipolar sagittal leads (ii) the SVEC III sagittal lead intermediate between the first and third classes and (iii) the grid showing greater uniformity and orthogonality than the four other leads

2 Nonuniformity expressed as arithmetic standard deviation of measured lead voltages supports the division into three classes It is 30 to 50 per cent in group (i) 16 to 24 per cent in the SVEC III sagittal lead and 4 to 8 per cent in the sagittal grid The standard deviation on a logarithmic scale of millivolts again separates the three groups (p = 0 001) and within the least accurate group (i) there is in most of the sets analyzed no significant difference in uniformity between the Frank McFee Parungao and bipolar leads

3 The means of sagittal lead voltages when the current source is x or y directed respectively used as a measure of nonorthogonality are 12 to 25 per cent in the

Frank, McFee-Parungao, and bipolar group, 12 to 30 per cent in SVEC III, and 4.3 to 5.7 per cent in the grid. The differences between the grid on the one hand and the 4 other leads on the other are significant ($p = 0.001$) in all heart sizes. Differences in orthogonality between leads other than the grid are statistically not significant in most of the samples.

4. The equation $M = A \cdot V / \rho$ derived previously in this laboratory is accurate within an error of ± 5 per cent in measuring the dipole moment of z-directed current source in the homogeneous torso model if A is the area of the 7 by 5 grid, V is the sagittal lead voltage, and ρ is the torso resistivity.

By the performance standards used in this study, the sagittal leads of the Frank and McFee-Parungao systems are not more uniform or orthogonal than is a simple bipolar sagittal lead. The SVEC III sagittal lead is more uniform but not more orthogonal. The parallel grid sagittal lead is more uniform and more orthogonal than any of the other leads tested.

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The mechanism of action of quinidine on the sinus node studied by direct perfusion through its artery

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Since the usual aim in the treatment of cardiac arrhythmias is restoration of sinus rhythm, it is obviously important to know the effect of quinidine on the sinus node. Utilizing an experimental preparation for direct perfusion of the sinus node through its own artery, we have investigated this effect in anesthetized dogs. The following is a report of our observations.

Method

Twelve dogs were anesthetized with intraperitoneal pentobarbital sodium (30 mg. per kilogram), the trachea was intubated for mechanical ventilation, and the chest was opened with a midline sternal splitting incision. The heart was exposed and cradled in the pericardial sac, and the right coronary artery was dissected free near the margo acutus. A small polyethylene cannula was then passed through an opening cut in the right coronary artery and into its sinus node branch.[1] Details of the procedure have been published previously.[2-4]

Quinidine gluconate diluted with Ringer's solution was prepared in concentrations of 0.001 to 100 μg per milliliter. Similar concentrations of quinidine were prepared in the dog's own fresh arterial blood. Acetylcholine chloride (1.0 μg/ml.) and l-norepinephrine bitartrate (0.1 μg/ml.) were prepared in Ringer's solution for injection into the sinus node artery. Injections into the sinus node artery were delivered from a hand syringe in 1.0 ml. volume in 30 seconds. This perfusion time for quinidine was based on three considerations: (1) the rapid uptake of quinidine, 95 per cent of which is cleared from the blood in from a few seconds to 5 minutes;[5,6] (2) experience in this experimental model with many other drugs indicating usual effects from 30 seconds of perfusion; (3) toxic effects obtained with 30 second perfusions of high concentrations of quinidine (see below).

The vagus nerve at the mid-cervical level and the stellate ganglion within the thorax were isolated for stimulation with an electronic rectangular wave stimulator before and periodically after injections of quinidine. Pressures were recorded with transducers from cannulas routinely placed in the central aorta and right atrium, along with a tachogram derived with an analog

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computer Through a slave circuit an electrocardiogram was recorded constantly at 25 or 50 mm per second during slow speeds (0 25 mm per second) on the master recorder Details of electrocardiographic complexes were followed on an oscilloscope during experiments and later analyzed from the electrocardiogram

Results

At concentrations of 1 0 µg/ml and below there was no significant direct effect of quinidine on the sinus node (Fig 1) At concentrations of 10 0 µg/ml there was slight acceleration of sinus rhythm (average of 10 per cent in 12 experiments) lasting 1 to 6 minutes No episodes of sinus arrest or other disorganization of sinus rhythm occured at 10 0 µg/ml Concentrations of 100 µg/ml produced significant slowing of sinus rhythm lasting 10 to 40 minutes (average 18 minutes) in 9 of 11 experiments In 5 of these 9 the effect was more profound than simple bradycardia indicated for there was sinus arrest with an escape A V nodal rhythm lasting 2 to 34 minutes (average 13 minutes) and followed by a sinus bradycardia which gradually accelerated until the return to control rate (Fig 2) The maximal negative chronotropic effect from 100 µg of quinidine appeared immediately in 7 of the 9 experiments but was delayed for 3 and 4 minutes in the other 2 After the bradycardia in 3 of these 9 experiments there was a slight acceleration of sinus rhythm (average of 10% over control rate) lasting 12 to 25 minutes

Approximately half of the injections of each concentration of quinidine were given in Ringer s solution and half in arterial blood Results obtained with quinidine diluted in Ringer s solution were not significantly different from those obtained with quinidine diluted in fresh arterial blood Except for the A V nodal rhythm described above intranodal quinidine produced no alteration of the P R interval nor of QRS duration or configuration there was no significant change in right atrial or central aortic pulses or pressure

To examine the anticholinergic effect of quinidine on the sinus node the right vagus nerve was stimulated before and periodically after each injection of quinidine In 8 dogs this was compared with the response of the sinus node to acetylcholine injected into the sinus node artery before and periodically after quinidine At all concentrations of quinidine there was a detectable anticholinergic effect which was most pronounced with often a complete cholinergic block at 10 and 100 µg/ml (Fig 3) In all instances the anticholinergic effect gradually subsided (Fig 4) with return to normal cholinergic response in from 30 to 50 minutes In 4 experiments the anticholinergic effect became maximal only 6 to 12 minutes after administration of the

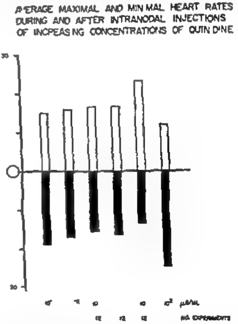

Fig 1 Except in high concentrations quinidine had little effect on the rate of the sinus node The ordinate indicates the number of beats per minute above or below the control heart rate (*C*) the white bars represent the average maximal heart rate seen after all the injections at the indicated concentrations and the black bars indicate the average minimal heart rate during or after the injections Sinus bradycardia occurs *during* injections of Ringer s solution or fresh autogenous arterial blood into the *sinus node artery and is followed by a brief period* of acceleration after the injection both of which are nonspecific responses The slowing and accelerating responses shown for the lower concentrations of quinidine here were identical to the responses during control injection of Ringer s solution or blood The maximal heart rate after injection of 10 µg/ml of quinidine was slightly greater than control injections whereas the minimal rate after 100 µg/ml was slightly less than control injections and furthermore was observed after the completion of the injection

Fig 2 An electrocardiogram of a typical response to injection of 100 μg/ml of quinidine into the sinus node artery. A is a control segment of tracing, B is recorded during the beginning of the injection and C near the end. D shows two continuous strips recorded 30 seconds after completion of the injection. Note the missing P-T_p segment which becomes apparent during the injection and which precedes the abrupt sinus arrest shown in D. After the sinus arrest there is an escape A-V nodal rhythm which persisted for 3 minutes, at which time sinus rhythm returned.

intranodal quinidine but in all the other experiments the effect was maximal within 2 minutes. This delayed onset of action as well as the occasional delayed appearance of maximal bradycardia suggest that the time of fixation (necessarily within 30 seconds in these experiments) and the time of maximal effect do not always coincide. On comparison of the response to vagal stimulation and to intranodal acetylcholine after quinidine there appeared to be little difference (Fig. 5). Quinidine blocked almost equally the depression of sinus rhythm from either cholinergic stimulus.

Although in general the concentrations of quinidine which slowed the sinus rhythm were also most effective in blocking cholinergic stimuli, neither the duration nor the degree of sinus bradycardia correlated directly with the anticholinergic effect. Similarly the onset of anticholinergic effect did not coincide with the onset of either acceleration or slowing of sinus rhythm after any concentration of quinidine. From these observations it seems that the direct and anticholinergic actions of quinidine are probably independent, although there may be some subtle indirect relationship.

In addition to the anticholinergic effect, quinidine also produced blockade of acceleration from either stellate stimulation or intranodal norepinephrine. As with the cholinergic blockade, there was an apparent adrenergic blockade at all concentrations but it was most distinct and easily followed after 1.0 μg and higher (Figs. 6-9). The duration of adrenergic blockade was 20 to 60 minutes, with the effect of the higher concentrations being the more prolonged, but the degree of blockade was usually incomplete since some acceleration from adrenergic stimulation (either by nerve or hormone) remained present. Maximal adrenergic blocking effect did not correlate with the direct effect of quinidine on the

sinus rate and as with the anticholinergic effect sometimes became maximal only several minutes after the injection of quinidine There was no significant difference between the blockade of acceleration from either stellate stimulation or intranodal injection of norepinephrine

Discussion

Direct effect of quinidine In concentrations considered to be within the therapeutic range in man [7,8] quinidine had little effect on the sinus node It is particularly significant that up to and including concentrations of 10 µg per milliliter there was no sinus arrest nor any disorganization of sinus rhythm However at 100 µg/ml which is above the therapeutic range the rate of the sinus node was usually depressed and its activity often arrested Between the concentrations of 10 and 100 µg/ml therefore a direct depressant effect of quinidine on the sinus node becomes manifest

In man blood concentrations of quinidine during its therapeutic use commonly reach 10 µg/ml and quite likely considerably higher levels are obtained during heroic efforts to control grave arrhythmias with intravenous quinidine It is precisely during such episodes that quinidine fatalities and sudden cardiac arrest are most likely to occur If one were to postulate a safe limit for the effect of quinidine on the normal sinus node 10 µg ml is probably that ceiling However the rapidity of uptake and fixation of quinidine from the blood by myocardium and other tissues necessarily limits the value of knowing the blood level of quinidine Furthermore response of the human sinus node to quinidine may be modified by two additional factors disease and concurrent use of other cardiac drugs Pericarditis[10] and coronary occlusion [11] for example have their own direct effects on the sinus node and how this relates to the direct effect of quinidine is uncertain Digitalis and its relationship to the effect of quinidine has received particular investigative attention [12,13] Experiments on the direct effect of digitalis on the sinus node studied in the same experimental preparation employed in this study of quinidine have demonstrated that moderate concentrations of digitalis may have either an accelerating or a depressing effect on the sinus node but concentrations which are definitely in the toxic range usually produced sinus arrest [14]

Although the effect of quinidine on the sinus rate in dogs has been reported as

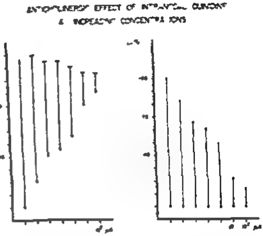

Fig 3 There was a direct relationship between the concentration of quinidine perfused into the sinus node artery and the blocking effect on vagal stimulation as shown here for one dog The absolute change in heart rate is presented on the left with the same experiments expressed as per cent change in heart rate on the right In these and similar graphs the vertical lines indicate the change in heart rate with the small bar at one end showing the rate before stimulation and the dot at the other end of the line representing the maximal response

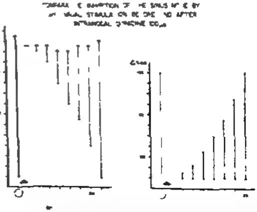

Fig 4 A typical experiment illustrating the duration of the vagal blocking effect of 100 µg /ml of quinidine perfused into the sinus node artery (*arrow*) is shown here A return to control response (C) occurred at 23 minutes Note that there was no relationship between the direct effect of quinidine on heart rate and its vagal blocking effect

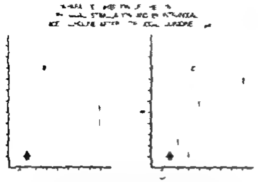

Fig. 5. A comparison of the anticholinergic effect of quinidine tested by right vagal stimulation (*RV on the left*) and by direct perfusion of acetylcholine 1.0 µg in 1.0 ml into the sinus node artery (*ACh on the right*). A control vagal stimulus and control injection of acetylcholine are indicated by *C* and quinidine was administered at the *point indicated* by the arrows; the time scale is minutes after the quinidine, with the vagal stimulus and injections of acetylcholine being alternated.

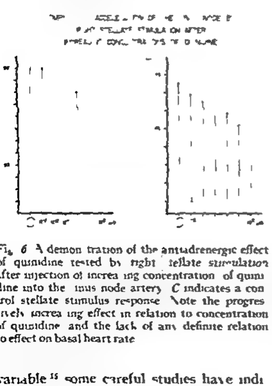

Fig. 6. A demonstration of the antiadrenergic effect of quinidine tested by right stellate stimulation after injection of increasing concentration of quinidine into the sinus node artery. *C* indicates a control stellate stimulus response. Note the progressively increasing effect in relation to concentration of quinidine and the lack of any definite relation to effect on basal heart rate.

variable,[15] some careful studies have indicated that quinidine has a cardiac accelerating effect.[11] Absence of an accelerating effect in other studies has been attributed to anesthesia of the experimental animals.[16] In view of the usual effect of numerous drugs perfused directly into the sinus node of anesthetized dogs,[11,2,13] we are reluctant at present to believe that quinidine acts exceptionally because of the anesthesia. It has been demonstrated with the systemic administration of quinidine to unanesthetized dogs that there is an increased extracardiac adrenergic activity, probably mediated through sympathetic pathways,[19] which may help explain some of the conflicting observations made on heart rate after the systemic administration of quinidine. However, our observation that quinidine also blocks (incompletely) the local effect of norepinephrine on the node indicates that there must be other factors as well.

One further observation may be made concerning the direct effect of quinidine and its potential role in sudden unexpected deaths. One of the recognized effects of quinidine is suppression of A-V conduction.[8] Whether quinidine also suppresses the inherent rhythmicity of the A-V node is unknown. The observation that 10 µg/ml of quinidine in our experiments did not stop the sinus node as pacemaker cannot be taken to mean that the same concentration necessarily spares the pacemaking potentialities of the A-V node. One may anticipate in view of the demonstrated effect of quinidine on A-V conduction that by the time blood levels are sufficient to suppress pacemaking by the sinus node there is similar suppression of the A-V node.

In a comprehensive study of quinidine and similar compounds, Dawes found that their antiarrhythmic effect was related to their local anesthetic effect.[1,22] The lack of significant influence on sinus rate in our experiments with quinidine concentrations calculated as near therapeutic levels suggests that if there is a local anesthetic effect on the node, it does not alter sinus rate.

Anticholinergic effect of quinidine. It has long been known from a variety of studies that quinidine blocks many effects of vagal stimulation.[8] In the treatment of atrial fibrillation this is a particularly useful action, since vagal stimulation is known to both enhance the development and prolong the duration of this arrhythmia.[23,4] It is hardly surprising that quinidine injected into the sinus node blocks the bradycardia from either vagal stimulation or intranodal injection of acetylcholine (Fig. 5). The fact that it opposes the action of

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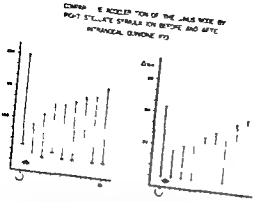

Fig 7 A typical experiment showing the duration of the antiadrenergic effect of 100 µg of quinidine *C* indicates a control response to stellate stimulation and the arrow marks the injection of quinidine into the sinus node artery Recovery occurs in about 76 minutes Changes in the basal heart rate do not correspond to the degree of antiadrenergic effect.

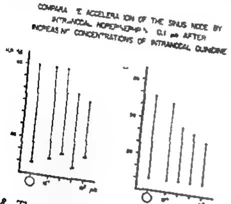

Fig 8 The antiadrenergic effect of quinidine is here demonstrated with injection of norepinephrine into the sinus node artery after injections of increasing concentrations of quinidine *C* indicates a control response to norepinephrine injected into the sinus node artery The antiadrenergic effect is similar to that seen with stellate stimulation although lower concentrations of quinidine have perhaps less antagonism of local norepinephrine than of stellate stimulation Note again the lack of correlation between the direct and antiadrenergic effects of quinidine

directly infused acetylcholine proves that quinidine does not exert its action by blocking the local release of acetylcholine or at least not by that means alone

The anticholinergic action of 10 µg of quinidine perfused directly into the sinus node is comparable in *duration* to the action of 10 µg of atropine administered in the same manner although the initial effect is regularly more profound with atropine [16] Both last about 30 minutes but the complete blockade of vagal stimulation occupies almost the first half of this time after atropine whereas the blockade by quinidine begins to wane within a few minutes after the injection

Although the anticholinergic action of quinidine on the atrial myocardial refractory period is opposite to the effect of digitalis (and the vagus both of which shorten it) it has been reported that both quinidine and digitalis produce a net loss of myocardial potassium [3] The duration of the chronotropic effect of digitalis perfused directly into the sinus node[11] corresponds closely to the period of myocardial potassium efflux [4] In our experiments the chronotropic effect of quinidine short of what were probably toxic concentrations was negligible but the anticholinergic effect had a duration which was analogous to the period of potassium efflux

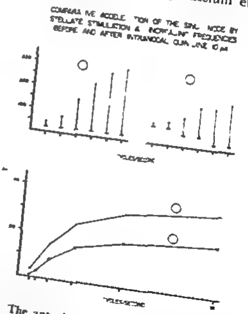

Fig 9 The antiadrenergic effect of quinidine was equally apparent at low and high frequencies of stellate stimulation as demonstrated in this experiment after the injection of 10 µg of quinidine into the sinus node artery The acceleration after the control stimuli in *A* was slightly less than that observed in most dogs but the parallel suppression of response apparent 3 minutes after the quinidine is clear in *B* The upper two graphs represent changes in absolute heart rate before (*A*) and after (*B*) quinidine and the lower graph combines the per cent change in heart rate before and after quinidine

from quinidine studied in heart lung preparations In view of this common action on potassium balance by both quinidine and digitalis it is possible to consider their difference in action on heart rate and on atrial myocardial refractory period as being due to their different relation to acetylcholine metabolism independent of effect on potassium However much remains to be examined concerning such a hypothesis

Of further interest pertinent to the effects of quinidine on the sinus node are the observations of Briscoe and Burn[7] with regard to the relationship between the actions of quinidine and acetylcholine on isolated rabbit atrial myocardium In their studies the addition of quinidine to baths containing atrial strips caused the rate of contractions to decrease and this action of quinidine was antagonized by acetylcholine They attributed this effect to a competition between quinidine and acetylcholine for the same receptor sites Whether their observations and interpretations concerning atrial myocardium also apply to the sinus node is uncertain however since the anticholinergic effect of quinidine observed in our studies was independent of its effect on pacemaking rate by the node At higher concentrations of quinidine (probably toxic levels) there was both a negative chronotropic and an anticholinergic effect but at lower concentrations of quinidine the latter was present without the former

Antiadrenergic effect of quinidine In contrast to the widely studied anticholinergic effect of quinidine its antiadrenergic effect is less well known Since catecholamines are known to shorten the atrial refractory period[11] and since this action is an obviously important factor which concerns both the pathogenesis and maintenance of cardiac arrhythmias the significance of information relating the effects of quinidine and adrenergic stimuli is readily apparent Catecholamines are known to increase the excitability of both atrial and ventricular ectopic foci[8] and have been shown to enhance the development of experimental atrial fibrillation[9] providing a second reason for the potential importance of the antiadrenergic effect of quinidine as applied to its use in the treatment of cardiac arrhythmias

From our observations with the sinus node one must conclude that an antiadrenergic effect of quinidine occurs at the same time and for approximately the same duration as the anticholinergic effect and that the two opposite effects are of comparable degree Whether this antiadrenergic effect in the sinus node can be applied to other myocardium in the atria atrioventricular conducting system or ventricles is uncertain For this reason it is difficult to interpret the mechanism of the antiadrenergic effect by quinidine on the sinus node from membrane potential and potassium balance studies made on other cardiac tissue The fact that the adrenergic block included response to either stellate stimulation or local infusion of norepinephrine indicates that quinidine does not simply block local release of norepinephrine but that its site of action is at the receptor level

Microelectrode studies of the sinus node indicate that norepinephrine and epinephrine increase the rate of depolarization during Phase 4[9] whereas quinidine in concentrations known to affect Purkinje fiber pacemakers does not cause an appreciable change in the slope of Phase 4 in the sinus node[15,16] Similarly direct perfusion of the sinus node with norepinephrine and other sympathomimetic amines has a marked accelerating effect[17] whereas quinidine at therapeutic concentrations has little or no effect (Fig 1) Thus like the anticholinergic effect of quinidine the antiadrenergic effect seems to occur independently of the direct chronotropic effect

Both digitalis and quinidine have an antiadrenergic effect and that of digitalis has been demonstrated after both systemic administration[11] and direct perfusion of the sinus node[12] The duration of this effect after either drug is comparable although the effect of digitalis is associated with distinct direct chronotropic action whereas that of quinidine (except in high concentrations) is not

Summary

Studied by direct perfusion of the sinus node through its artery quinidine has three actions direct anticholinergic and antiadrenergic The direct action of quinidine is insignificant at concentrations be

low 10.0 µg per milliliter but causes suppression of sinus activity at 100 µg per milliliter. The anticholinergic and antiadrenergic actions occur concurrently and are unrelated to the direct action; both of these effects increase in direct relation to the concentration of quinidine. Since the autonomic blocking effect includes both nerve stimulation and the administration of local neurohormones, this action of quinidine occurs at the receptor site and is not due to inhibition of local release of effector substance.

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Case reports

Reversed reciprocating paroxysmal tachycardia controlled by guanethidine in a case of Wolff-Parkinson-White syndrome

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Although paroxysmal tachycardias are frequent complications of the Wolff-Parkinson-White (WPW) syndrome, many are refractory to treatment. To our knowledge, the prevention of paroxysmal tachycardia by guanethidine when other forms of treatment were ineffective has not been reported previously.

Case report

D. W., a 22-year-old white man, was admitted to the Multnomah County Hospital on Oct. 4, 1961, seeking relief from episodes of paroxysmal tachycardia which had occurred since he was 8 months old. During the preceding 2 years the attacks had been more frequent and prolonged. The episodes of tachycardia often persisted for several days, and during the past 2 years tachycardia had been present more than half the time. The factors which precipitated or terminated the attacks were unknown, except that occasionally a Valsalva maneuver would restore normal heart rate.

At the age of 10 months he had been hospitalized for an unusually prolonged episode, and at that time his parents were told that his electrocardiogram was abnormal. During his childhood and youth there were numerous attacks of tachycardia, but usually of short duration. Recently he had been so incapacitated that he had been unable to work. There was no history of any other significant disability.

The blood pressure was 100/65 mm. Hg, the pulse was 66 per minute, and no cardiac enlargement or murmurs were present.

Hemoglobin, erythrocytes, leukocytes, serology for syphilis, routine urinalysis, fasting blood glucose, protein-bound iodine, sedimentation rate, blood urea nitrogen, and electrolyte determinations were within normal limits. Radiograms of the thorax showed normal pulmonary vasculature and heart size. An electrocardiogram was characteristic of the WPW syndrome, type A (Fig. 1).

On the next day a supraventricular tachycardia at a rate of 156 beats per minute occurred (Fig. 2). Carotid sinus massage and Müller and Valsalva maneuvers were ineffective, and the attack terminated spontaneously after several hours.

During his hospitalization of 24 days and subsequently during 5 months of care in the outpatient clinic, the episodes of tachycardia were not prevented by full doses of digitalis, quinidine, procaine amide, Prostigmine, phenobarbital, diphenylhydantoin sodium, or a number of combinations of these drugs. Reserpine, 0.25 mg. four times daily, prevented the attacks for a month, but then was ineffective even in larger doses.

On April 4, 1962, he was hospitalized for a supraventricular tachycardia that had persisted for 3 days. A bilateral stellate ganglion block with 1 per cent Xylocaine was performed, and sinus rhythm occurred for a period of 16 hours after the block.

Guanethidine, 10 mg., with gradually increasing dosage, and phenobarbital, 30 mg. twice daily, were then started. He has received 50 to 60 mg. of guanethidine daily for the past 11 months, with only rare episodes of tachycardia except when the dosage was reduced deliberately in order to observe the effect.

No symptoms of vertigo, syncope, or hypotension developed, and the blood pressure readings

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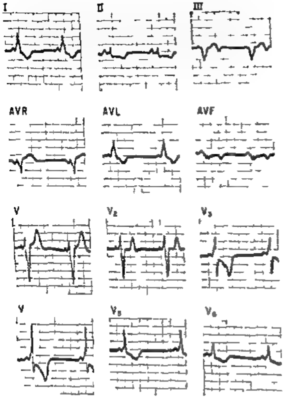

Fig. 1. Sinus bradycardia, rate 47. P-R = 0.11 sec. QRS = 0.14 sec. WPW complexes type A are present.

in the recumbent and standing positions showed only minor variation from the pretreatment level.

Comment

Guanethidine [2-(octahydro-1-azocinyl)-ethyl] guanidine sulfate (Ismelin)* was introduced for the treatment of hypertension by Page and Dustan. A protracted blocking action on postganglionic nerve terminals of the sympathetic nervous system has been demonstrated in animals.[3] In clinical use, guanethidine has been effective in lowering the blood pressure in patients with hypertension, and the most pronounced side effects have been related to the unopposed action of parasympathetic activity.[4-6] Many patients receiving the drug have bradycardia, although none to a troublesome degree.[4-6]

In this patient the prevention of tachycardia for over a month with reserpine and the conversion of his tachycardia to a sinus rhythm during a bilateral stellate ganglion block procedure suggested that guanethidine would be effective because of its blocking of sympathetic activity.

When the daily dose of guanethidine was 30 mg., the rhythm consisted of sinus beats alternating with paroxysms of tachycardia which lasted from 8 to 17 beats. On any one day the number of beats in a paroxysm was usually the same or did not vary by more than one or two beats.

With a daily dose of 40 mg. the periods of normal sinus conduction were longer and the paroxysms of tachycardia shorter, usually 3 to 7 beats. A regular daily dosage of 50 mg. eliminated the attacks unless an upper respiratory infection was present. When this occurred, 60 mg. would be required for a few days.

On some days, for no apparent reason, sinus rhythm with normal conduction would be present, and on other days the QRS complexes would be of the WPW type.

If the conduction was of the WPW type, mild exercise, such as 10 sit-ups, would convert the WPW complexes to normal

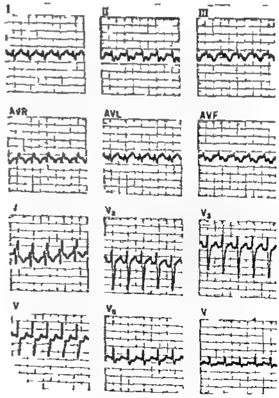

Fig. 2. Supraventricular tachycardia ...

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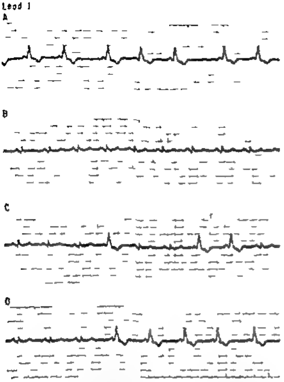

Fig. 3. All tracings are Lead I. Guanethidine dosage, 50 mg. daily. *A* shows sinus arrhythmia at a rate of 55 beats per minute and WPW complexes. *B*, Recorded after 10 sit-ups, demonstrates the increase in rate to 74 beats per minute and the change to normal conduction. *C* and *D*, A continuous strip taken after 30 seconds of rest, shows the change from normal conduction back to the WPW complexes. P-J interval during normal or WPW type of conduction is 0.27 sec.

conduction as the rate increased. On resting after exercise there would be an intermittent appearance of WPW complexes and finally all of the complexes would be of the WPW type as the rate slowed. Fig. 3 illustrates the WPW type of conduction at rest, normal conduction immediately after exercise, and the return to the WPW form of excitation during rest in the postexercise period.

Relationship of guanethidine dosage and reversed reciprocating paroxysmal tachycardia. The pattern of heart beating that occurred when the patient was receiving an inadequate dosage of guanethidine, such as 30 or 40 mg. daily, is characteristic of reversed reciprocating paroxysmal tachycardia.[7,9]

An analysis of a paroxysm is illustrated in Fig. 4, when the patient was taking 30 mg. of guanethidine daily. Commencing with a sinus P wave, the impulse is conducted with a P-R interval of 0.17 sec. and records QRS complex 1. The impulse returns from the A-V node to record a retrograde P wave at an R-P' interval of 0.13 sec. The impulse returns once again anterogradely to the ventricles (P'-R' interval of 0.21 sec.) to record the second QRS complex. The impulse returns again from the A-V node to record a retrograde P' wave at an R-P' interval again of 0.13 sec. and further returning anterogradely (P'-R interval of 0.22 sec.) to record QRS complex 3. The cycle continues and ends with a QRS complex followed by an inverted P wave. The R-P' interval of 0.13 sec. is constant throughout the cycle.

In Fig. 5, when the patient was receiving 40 mg. of guanethidine daily, the paroxysms are shorter. Each cycle ends with a QRS complex and an inverted P wave does not follow the last QRS.

The series of beats in Fig. 4 ends in a different way than in Fig. 5. An inverted P wave follows the last QRS in Fig. 4, but does not follow the last QRS in Fig. 5. Theoretically, when either antegrade conduction through the A-V node or retrograde conduction through a hypothetical anomalous pathway[11,12] is blocked, the series ends.

Discussion

In reporting a case of reversed reciprocating paroxysmal tachycardia, Schamroth[7] postulated that the three basic requirements for this rhythm are: (1) an anomalous pathway, (2) unidirectional block in the anomalous pathway due to its long refractory phrase, and (3) a degree of A-V block in the junctional tissues. Although the case cited by Schamroth was not accompanied by the WPW syndrome, he suggested that a similar mechanism might be responsible for the attacks of tachycardia that occur in anomalous atrioventricular excitation. He explained that P waves may not be observed because of refractoriness of the atria.

In this patient with the WPW syndrome and episodes of reversed reciprocating paroxysmal tachycardia with retrograde activation of the atria, the findings are in accord with Schamroth's hypothesis.

The reciprocal tachycardia occurred only when WPW complexes were absent and normal conduction through the A V node was present demonstrating unidirectional block of the anomalous pathway.[10] According to Wolff[10] normal conduction in a person who has WPW complexes at other times indicates that the anomalous pathway is relatively refractory when the impulse from the atria arrives at the A V node. The stimulus is conducted by normal pathways through the A V node and then is able to return in a retrograde manner to the atria via the anomalous pathway which now has had time to recover from its refractory state. Wolff has commented that in the presence of WPW complexes the anomalous pathway necessarily would be discharged in an antegrade direction at approximately the same time as the A V node and hence both pathways would be refractory to retrograde conduction of the

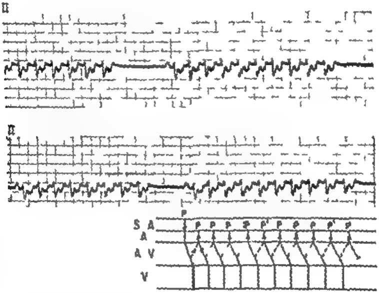

Fig 4 Guanethidine dosage 30 mg daily. Continuous strip of Lead II with a graphic analysis of a paroxysm of reversed reciprocating paroxysmal tachycardia. The dashed lines represent retrograde conduction via a theoretical anomalous bundle. S A Sinoatrial node. A Atria. A V Atrioventricular node. V Ventricles. The first normally conducted impulse in its passage through the A V node and to the ventricles returns in a retrograde direction through the anomalous bundle. It discharges the atria in a retrograde manner and returns to the A V node. The cycle continues until the return of the impulse through the A V node is blocked. (See text.)

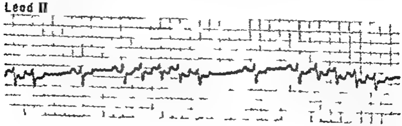

Fig 5 Guanethidine dosage 40 mg daily. Lead II. The paroxysms of tachycardia are shorter than when the dosage was 30 mg daily. The paroxysms do not end with a retrograde P wave as in Fig 4. The cycle terminates when conduction via the anomalous pathway is

impulse, thus preventing the occurrence of the tachycardia.

During the tachycardia the P-R interval consistently demonstrated prolongation, being 0.21 sec. or longer, which indicates that some degree of A-V block was present. The P-R interval during normal conduction was in the range of 0.17 sec. The delay in the A-V junctional tissues theoretically allows time for recovery of the anomalous bundle and conduction in a retrograde direction.

There was a definite decrease in the duration of the paroxysms of tachycardia until they were eliminated by increasing doses of guanethidine. On three occasions the amount of guanethidine was deliberately decreased to 30 mg. daily, and then increased to 40 mg., and then to 50 mg. daily. The same pattern of relatively long runs of tachycardia separated by sinus beats occurred each time with the administration of 30 mg. daily. As the dosage was increased gradually back to the maintenance level, the periods of tachycardia became shorter until they were eliminated. The effect of guanethidine in shortening or eliminating the attacks of tachycardia with increasing dosage of the drug was consistent and reproducible.

The blocking of sympathetic activity by guanethidine apparently exerted a significant influence on the refractoriness of the conduction pathways of the A-V node and the anomalous bundle. An indirect effect due to relatively unopposed vagal activity may have been the principal reason for control of the tachycardia, since a sinus bradycardia and a marked sinus arrhythmia have been present most of the time since the patient began taking guanethidine.

An accepted property associated with increased vagal activity is its ability to lengthen the refractory period of the A-V node, whereas the effect of vagal stimulation on the anomalous pathway[10] in the WPW syndrome has not been definitely established.

Summary

A case of reversed reciprocating paroxysmal tachycardia in a patient with the WPW syndrome is reported. The tachycardia was controlled by guanethidine. The blocking of sympathetic activity, with resultant predominant vagal influence on the conduction pathways of the A-V node and the anomalous bundle, is offered as an explanation for the control of this arrhythmia.

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Pulmonary hypertension after Blalock-Taussig anastomosis

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Pulmonary hypertension due to severe pulmonary vascular obstruction is a rare late complication of the systemic-pulmonary artery anastomosis operation for Fallot's tetralogy. Ten cases have been reported previously,[1-9] and we here report a further example in which cardiac catheterization was repeated after a 5 year interval. This condition is of great importance in the selection for subsequent total correction of Fallot's tetralogy of patients who have previously undergone anastomotic operation. It is also of great interest in regard to the problem of the pathogenesis of obstructive pulmonary vascular disease complicating congenital heart lesions.

Case report

D. Y., a girl born in 1937, was first noted to be cyanotic after exercise at 1 year of age. She was not cyanotic at rest, but squatted frequently with any active exercise and also had marked fatigue on effort. When seen at The Johns Hopkins Hospital in 1951, she had slight clubbing of the fingers and toes and was not cyanotic at rest. A Grade 4/6 harsh systolic murmur was widely heard, with a fairly marked systolic thrill along the left sternal border and in the suprasternal notch. The second sound was loud and unsplit. There was no diastolic murmur. The blood hemoglobin concentration was 11.5 Gm./100ml., the red blood cell count was 5.1 million per cubic millimeter, and the hematocrit was 47 per cent. Chest x-ray films showed normal heart size with a concavity in the pulmonary conus region, well-marked hilar shadows, and unusually clear peripheral lung fields. The electrocardiogram showed right axis deviation and right ventricular hypertrophy. Cardiac catheterization and angiocardiography were not performed. The diagnosis of Fallot's tetralogy was made, and the hypochromic anemia was thought to explain the disability out of proportion to the cyanosis.

Left subclavian-pulmonary artery anastomosis was performed on Jan. 22, 1951. The pulmonary artery was large, at least 15 mm. in diameter, but easily compressible, which suggested a low pulmonary arterial pressure. The subclavian artery was of moderate size, and a vigorous thrill was felt over the pulmonary artery after release of the clamps.

The postoperative course was uncomplicated. Ten days after operation the continuous murmur which had previously been present could no longer be heard. Subjective improvement was minimal. The hematocrit was 46 per cent. Oximetry revealed a resting arterial oxygen saturation of 93 per cent, which fell to 72 per cent during exercise. The anastomosis was thought to have closed, and on March 1, 1951, a right subclavian-pulmonary artery anastomosis was performed. The postoperative course was complicated by fever, pericarditis, pleurisy with effusion, and possible thrombophlebitis in the legs. When discharged from the hospital 2 months after the operation, the patient was able to increase her walking distance markedly. A loud continuous murmur was present over the right upper chest, and a soft continuous murmur was present over the left upper chest. Her color was excellent. The heart was normal in size by x-ray examination, but slightly

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During the tachycardia the P-R interval consistently demonstrated prolongation, being 0.21 sec. or longer, which indicates that some degree of A-V block was present. The P-R interval during normal conduction was in the range of 0.14 sec. The delay in the A-V junctional tissues theoretically allows time for recovery of the anomalous bundle and conduction in a retrograde direction.

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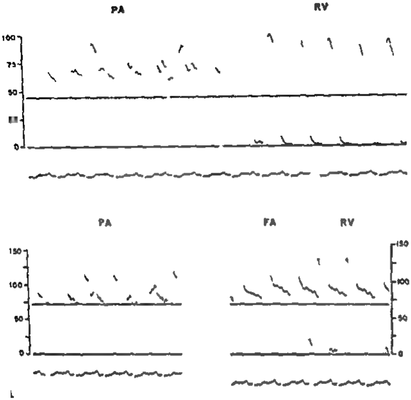

Fig 2 *Top* Pre ure record during withdrawal of the cardiac catheter from the pulmonary artery to the right ventricle showing no evidence of the severe pulmonary stenosis which i present *Left* Pulmonary arterial pressure is equal to systemic arterial pressure *Right* Simultaneous pressure records from the right ventricle and femoral artery showing equal systolic pressures

Table I Cardiac catheterization data in Patient D I with severe pulmonary hypertension after bilateral Blalock Taussig anastomoses performed in 1951 for Fallot s tetralogy

Parameter	*Dec 3 1959*	*Aug 14 196*
Body surface area (M²)	1 57	1 57
Right atrium Pressure (mm Hg)	5	6
Oxygen saturation (%)	60 5	56 1
Right ventricle Pressure (mm Hg)	143/3	135/5
Oxygen saturation (%)	61 5	60 3
Pulmonary artery Pressure (mm Hg)	134/77	135/79
Oxygen saturation (%)	4 0	9 8
Aorta Pressure (mm Hg)	148/77	125/80
Oxygen saturation (%)	75 0	81 2
Oxygen capacity (vol %)	24 3	25 4
Pulmonary flow (L /min /M²)	3 0	3 7
Systemic flow (L /min /M²)	4 4	4 1
Pulmonary—systemic flow ratio	0 7	0
Pulmonary resistance (mm Hg/L /min /M²)	31 7	26
Systemic resistance (mm Hg/L /min /M²)	21 6	23
Pulmonary/systemic resistance ratio	1 5	1

tocrit was 55 per cent. Otherwise the physical findings and the roentgenographic and electrocardiographic appearances were unchanged. On this occasion the cardiac catheter was passed via the right ventricle and main pulmonary artery to the distal right pulmonary branches, and the presence of pulmonary hypertension equivalent to systemic pressure level was definitely confirmed. The pressure recorded during withdrawal from the pulmonary artery to the right ventricle showed no evidence of an infundibular chamber or pulmonary stenosis (Fig. 2). The right ventricular cineangiogram showed virtually complete right-to-left shunting at the ventricular level, but on very close inspection of the cinefilm a trace of contrast medium could be seen passing through the pulmonary stenosis. There was some evidence of aortic insufficiency. A cineaortogram showed wide patency of both subclavian-pulmonary anastomoses, both of which appeared to be unusually large, and virtually all of the pulmonary blood flow appeared to enter by this route. Bronchial collateral flow to the lungs was not prominently seen.

Because of the demonstration of a very high pulmonary vascular resistance, a corrective operation was not advised. During an additional year's follow-up, there has been no important clinical change.

Discussion

The pulmonary vascular obstruction responsible for the severe pulmonary hypertension in this case either existed prior to the anastomotic operation, developed immediately thereafter, or developed years later as a late complication. The somewhat enlarged central pulmonary arteries before operation were an unusual feature, and the presence of obliterative changes in the pulmonary vessels in untreated Fallot's tetralogy is well recognized[6-8]; however, significant pulmonary hypertension before operation in this patient seems to have been very unlikely. The early disappearance of the continuous murmur in an anastomosis later shown to be widely patent may suggest that pulmonary hypertension became established within a few days of the first operation. The failure of cardiac enlargement and pulmonary overcirculation to develop in spite of large bilateral anastomoses may also suggest this. However, the substantial clinical improvement which lasted 5 years, and the rather rapid deterioration which occurred in 1958, suggest that progressive pulmonary vascular obstruction developed as a late complication. In fact, all three of these probably took place in some degree. Stenosis of a pulmonary artery branch might also cause pulmonary hypertension in a case like the present one, but angiography appeared to rule this out.

In the previously reported cases of pulmonary hypertension after anastomotic operations, unusually large anastomoses have been a *common* feature (Table II). In 6 cases the operation was an aortopulmonary anastomosis of the Potts type, a technique which is very likely to produce an excessively large communication, and 3 of these were performed in patients who were 16, 26, and 27 years of age. One patient, like the patient reported on here, had bilateral subclavian-pulmonary artery anastomoses of the Blalock-Taussig type. One patient had a Potts operation and later a right Blalock-Taussig operation. Only 2 patients have been reported to develop pulmonary hypertension after a unilateral Blalock-Taussig operation; in one of these the subclavian arteries were noted at operation and at subsequent autopsy to be unusually large, and the other patient was 37 years old at the time of operation. Thus, no case has been reported in which severe pulmonary hypertension followed a unilateral Blalock-Taussig operation of the usual size performed at the usual age in infancy or early childhood. An unusually large aortopulmonary communication appears to be necessary for the development of obstructive pulmonary vascular disease after this operation. Certainly, the great majority of patients have normal pulmonary arterial pressure after this operation. For example, Moller[4] studied 44 unselected patients and found normal pulmonary arterial pressure in all.

In addition to anastomoses of large size, some of the patients with late pulmonary hypertension may have had moderately elevated pulmonary vascular resistance before operation, but no data are available to support this view. The clinical features and the appearance of a continuous murmur in all cases after operation suggest that if the pulmonary vascular resistances were elevated at the time of operation, they were not raised to systemic levels, and one must suppose that this occurred later, possibly as a response to the increased pulmonary flow. Indeed, McGaff and associates[5] considered these cases to be a

demonstration of the general hypothesis that increased pulmonary blood flow leads to obstructive pulmonary vascular disease.

The outstanding diagnostic features of pulmonary hypertension complicating Fallot's tetralogy after anastomotic operation are the return of dyspnea, cyanosis, and clubbing, enlargement of the central pulmonary artery shadows, and hemoptysis. Late clinical deterioration with return of dyspnea and cyanosis is of course much more commonly due to a shunt of inadequate size.[10,11] Enlargement of the pulmonary arteries is more commonly due to a shunt of excessive size, pulmonary blood flow is markedly increased with little or no pulmonary hypertension. Such patients are usually acyanotic.[3] Hemoptysis is a particularly valuable clue because this symptom in patients with congenital heart disease usually indicates severe pulmonary hypertension. Its occurrence in our patient led to the studies which revealed her present circulatory problem. In some cases the diagnosis during life must rest on such clinical clues since it may be impossible to enter the pulmonary artery during cardiac catheterization for direct confirmation of the pulmonary hypertension.

The systolic and diastolic murmurs in the patient whose case is presented in this paper were a source of some confusion. These were interpreted by some as a continuous murmur which suggested that subclavian-pulmonary artery shunts were still functioning and delivering blood to a low pressure, low resistance pulmonary vascular bed. The presence of a moderately wide pulse pressure and femoral arterial pistol shot sounds tended to support this view. Others interpreted the murmurs as to and fro rather than continuous, and the phonocardiographic appearance supported this, as did the location of greatest intensity in the third left intercostal space (Fig. 3). The diastolic murmur and bounding arterial pulse in this patient may have been due to aortic insufficiency from the dilated aorta, as was probable in Case II of Ross and associates[1] in which pulmonary atresia was found at autopsy. A regurgitant murmur across the pulmonary valve is also a possible explanation, especially when valvular stenosis is present.

Severe pulmonary stenosis without a pressure gradient across the pulmonary valve is a hemodynamic paradox which may occur when, in addition to the pulmonary stenosis, there is an aorto-pulmonary shunt and a raised pulmonary vascular resistance so that severe pulmonary hypertension is present. In a previously

Table II. Previously reported cases of severe pulmonary hypertension due to increased pulmonary vascular resistance after systemic pulmonary anastomotic operation for Fallot's tetralogy

Author	*Age at operation (yr.)*	*Surgical procedure*	*Method of study*	*Pulmonary arterial pressure (mm. Hg)†*	*Pulmonary vascular resistance*
Ross et al.[1]	27	Potts	Autopsy	—	—
	6½	Blalock	Autopsy	—	—
McGaff et al.[6]	13	Left Blalock			
	17	Right Blalock	Catheterization	111/79	0.45
	8	Right Blalock	Catheterization	106/63	1.0*
	26	Potts	Catheterization	115/76	1.0*
Leeds[7]	37	Potts	Operative pressure	135/85	—
Wagenvoort et al.[8]	1½	Right Blalock			
	2	Potts	Autopsy	—	—
Paul et al.[4]	?	Potts	Catheterization	45†	5.0*
	?	Potts	Catheterization	75†	15.8‡
	?	Potts	Catheterization	85†	18.0*

*Pulmonary vascular resistance expressed as the ratio of the pulmonary vascular resistance to the systemic vascular resistance.
†Pulmonary artery mean pressure mm. Hg.
‡Pulmonary vascular resistance expressed in units (mm. Hg/L./min.).

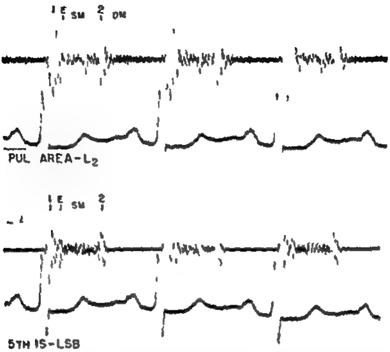

Fig. 3. Phonocardiogram in the second left intercostal space (*above*) and in the fifth left intercostal space (*below*). There is a loud first sound (*1*), an early systolic ejection sound (*E*), and intense full length diamond shaped systolic murmur (*SM*), and a loud single second sound (*2*). In the second intercostal space there is a long diminuendo diastolic murmur. The appearances suggest to-and-fro murmurs rather than a continuous murmur.

reported instance there was a ventricular septal defect, infundibular pulmonary stenosis, and a large patent ductus arteriosus, although the results of cardiac catheterization suggested only ventricular septal defect with pulmonary hypertension.[1] Such cases may also lead to an error in angiographic interpretation. Pulmonary atresia may be suggested because no contrast medium is seen to pass through the pulmonary stenosis; in fact, a channel is present but little or no flow occurs because of the high pressure beyond and the marked tendency to preferential shunting through the large aorto-pulmonary communication. This should be considered in the evaluation of reported cases of acquired pulmonary atresia.[13,14]

Successful surgical treatment of Fallot's tetralogy with severe pulmonary hypertension after anastomotic operation has not been reported, and in most cases the condition appears to be inoperable. The operative risk in such patients must be high, and unless the pulmonary vascular obstruction is reversible, a persistence of severe pulmonary hypertension would be expected and could be more incapacitating than the unoperated condition. There are no data which bear directly on the critical question of whether this type of obstructive pulmonary vascular disease is in fact reversible. Ferencz[15] and Fragoyannis and Kardalinos[3] showed that the obstructive vascular lesions in untreated Fallot's tetralogy, stemming from thrombosis due to polycythemia and reduced sluggish blood flow, are reversible after systemic-pulmonary anastomosis. Braunwald and associates[16] showed that surgical abolition of shunts at the aorto-pulmonary level was followed by substantial reversal of pulmonary vascular obstruction, whereas no significant fall in pulmonary vascular resistance followed abolition of shunts of intracardiac type. Thus, there is some basis for the hope that pulmonary vascular obstruction after systemic-pulmonary an-

astomosis may be reversible in some cases when a complete repair is accomplished

Summary

A patient with Fallot's tetralogy who had bilateral subclavian pulmonary anastomoses at 12 years of age was found to have severe pulmonary hypertension 8 years later. The pressure and vascular resistance in the pulmonary circulation were equal to the systemic circulation. The pulmonary stenosis was severe and virtually all the pulmonary blood flow occurred via the anastomoses. Despite severe pulmonary stenosis no systolic pressure gradient was demonstrated across the right ventricular outflow tract and the angiocardiographic picture simulated that of pulmonary atresia. Systolic and diastolic murmurs at the upper left sternal border were present simulating the usual subclavian pulmonary anastomotic murmur but probably arising from aortic insufficiency. Hemoptysis and gross enlargement of the pulmonary artery were clinical clues pointing to the true situation which was revealed by cardiac catheterization. Repeat study 3 years later showed slight clinical and hemodynamic improvement.

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Clinical pathologic conference

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Clinical summary

This 29 year-old Negro woman was admitted to Presbyterian-St. Luke's Hospital on March 11, 1963. She had been well until 10 months prior to admission when she developed a blister-like pruritic rash on the extremities. She was 2 months pregnant at the time. The lesions were at first thought to be tuberculids. The rash gradually cleared and left small depigmented areas. A normal full-term child was delivered in another hospital in October, 1962. Postpartum, she weighed 165 pounds. In November, 1962, nausea, vomiting, and epigastric pain appeared. She was admitted to another hospital but anorexia and vomiting persisted and her weight dropped to 100 pounds. She had hematemesis intermittently. Examination revealed many lesions which were described as dried pustules on the arms. Gastrointestinal x-ray films and proctoscopy were negative. A rectal biopsy disclosed a mild chronic colitis. Biopsy of an axillary lymph node showed a nonspecific lymphadenitis. Peritoneoscopy showed no abnormality. She was discharged from the hospital in January, 1963, but was readmitted 2 weeks later. The loss in weight and abdominal pain continued for the following 2 months until she weighed 70 pounds. The skin rash now involved the chest. She became bedridden and incontinent of urine and feces. The development of dyspnea a few days prior to her admission to Presbyterian-St. Luke's Hospital prompted her family to bring her to the emergency room.

The past history revealed that she had been in the Chicago Municipal Tuberculosis Sanatarium in 1959 and again in 1960. A diagnosis of advanced pulmonary tuberculosis was made. The upper lobe of the left lung was resected and she was treated with chemotherapy until February, 1962, at which time the disease appeared to be inactive. The chest x-ray film was stable at that time and several sputa were negative on culture for tubercle bacilli. She had had 7 pregnancies and had 6 living children and 1 spontaneous abortion.

The family history disclosed that her mother had died at age 41 of heart disease and that her father had died at age 57 of a cerebral vascular accident. There were 11 siblings, one of whom had an enlarged heart. There was no family history of diseases of the skin.

On examination she was acutely ill and emaciated. The respirations were 28 and she had a loose cough. The pulse was 140 and regular. The systolic blood pressure was 50 mm. Hg by palpation. Korothoff sounds could not be heard. There were vitiliginous spots on the forearms. These had a depressed porcelain white center with a slightly raised red border. Other lesions were described as papules. The tongue was dry and the papillae were absent. The veins of the neck were not distended. The thyroid gland was not enlarged. There were no palpable enlarged lymph nodes. Examination of the lungs revealed bilateral rhonchi. The heart was not enlarged and there were no significant murmurs. There was slight tenderness in the right upper quadrant of the abdomen but no organomegaly or rigidity. Bowel tones were present. Pelvic and rectal examinations were negative. The extremities were normal except for the skin lesions and the marked emaciation. Bilateral Babinski signs were present and the deep tendon reflexes were absent.

The blood hemoglobin was 6.7 Gm. per cent and the hematocrit was 21. Red blood cell constants indicated that this was a normochromic normocytic anemia. The white blood cell count was 15,500 with 24 neutrophils, 55 band, 13 lymphocytes, and 8 monocytes. The urinalysis showed proteinuria (++) and 50 to 60 white blood cells with 15 to 20 red blood cells per high power field. No acid-fast bacilli were found in the sputum and gastric washings. Cerebrospinal fluid was negative for tubercle bacilli on culture. Skin tests for histoplasmosis, blastomycosis, and coccidioidomycosis were negative. There was no occult blood in the stool. Proteus, Pseudomonas, and Aerobacter microorganisms were grown from a throat culture. The C-reactive protein was 2 plus. Sheep cell agglutination and the latex fixation tests were negative. The protein bound iodine was 4.8. The serum iron was 60 μg per cent and the iron binding capacity was 250 μg per cent.

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The serum Kahn and Wassermann tests were negative. The plasma cholesterol was 196 mg. per cent. The blood urea nitrogen was 179 mg. per cent, the serum sodium 129, serum potassium 3.0, chloride was 102, and CO_2 was 14.2 mEq. per liter. Spinal fluid contained 92 white blood cells and 25/500 noncrenated red blood cells. The blood urea nitrogen later dropped to 58 mg. per cent, and the sodium and chloride rose. The chest x-ray film showed an infiltrate in the left mid lung field and loculated fluid at the left apex. Bone marrow was reactive but not diagnostic. The serum electrophoresis showed an albumin of 2.2 Gm. per cent with normal globulins. An electrocardiogram showed nonspecific ST-T abnormalities. She was transfused with 3 units of whole blood, and the hematocrit rose to 33. She was treated with intravenous fluid, prednisolone, INH (isoniazid), streptomycin, and penicillin and seemed to improve. A dermatology consultant thought that the skin lesions were manifestations of tuberculosis. On March 13, 1963, she abruptly became semicomatose. A lumbar puncture was attempted, but bloody cerebrospinal fluid was obtained. Nuchal rigidity developed. She responded to pain only. On March 14, 1963, anuria developed. She became hypotensive and died in coma.

Discussion

DR. PHELAN: This young woman with a previous history of pulmonary tuberculosis presents a diagnostic problem which is characterized by skin lesions, gastrointestinal symptoms, and loss of weight. One of the first considerations would be tuberculous involvement of the skin and bowel. The description of the skin lesions does not seem to be typical of lupus vulgaris, in which there are reddish-brown patches composed of nodules with an apple-jelly color. These are commonly on the face. The skin lesions of this patient were not on the face but were limited to the extremities and upper trunk. Also, the lesions existed in various stages from papules to a form with white centers and a red border. There is no mention of lesions underlying the skin such as occur in some cases of tuberculosis. Early in her course it was thought that she might have tuberculids, but the lesions as described do not seem to have the characteristics of tuberculids. Other evidence against the diagnosis of tuberculosis was that the sputum, gastric washings, and spinal fluid showed no acid-fast bacilli on smear, and the cultures were negative for tubercle bacilli.

Some consideration should also be given to the deep mycotic infections. These usually are characterized by chronic skin ulcerations and draining sinuses, which our patient did not have. Also, skin tests for histoplasmosis, blastomycosis, and coccidioidomycosis were negative.

Collagen diseases must be included in the differential diagnosis, and of these systemic lupus erythematosus should be strongly considered. This patient's disease involved several organ systems. However, neither the skin lesions nor the gastrointestinal symptoms are typical of lupus erythematosus, and the lupus erythematosus cell preparations were negative. The skin lesions described do not seem like those typical of scleroderma or polyarteritis, although in these diseases there are a variety of changes in the skin.

Leukemia and the lymphomas may cause skin lesions and involve the gastrointestinal tract. However, the spleen was not palpable, the blood smear showed no abnormal cells, and the bone marrow showed no evidence of leukemia. There were no palpable enlarged lymph nodes, and biopsy of an

Fig. 1. This shows a small cutaneous vascular channel with perivascular lymphocytic infiltration.

Fig. 2. This section of a healed cutaneous lesion shows epidermal atrophy, absence of appendages, and homogenization of the dermal intercellular matrices.

axillary node done about 2 months before her death showed no evidence of disease.

Thromboangiitis obliterans may cause nodules that become necrotic and ulcerate, and this disease occasionally involves the superior mesenteric artery, giving intestinal symptoms. However, our patient was not a male, and the typical findings of this disease were not present.

There is a disease described by Degos and given his name which has characteristic skin lesions and intestinal symptoms. Degos called the disease malignant atrophic papulosis. The disease begins with a papular eruption scattered over the trunk and extremities. The face, scalp, palms, soles, and mucous membranes are spared. The papules are 2 to 10 mm. in diameter and are pale rose or yellowish gray in color. The papule becomes umbilicated in time, and the depressed center develops a porcelain white tint with scales. The margin remains red. The porcelain white center is characteristic of the disease. The cutaneous phase of the disease lasts for a few weeks to 3 years, during which time several crops of papules appear. The abdominal phase of the disease usually appears abruptly and is characterized by abdominal pain, vomiting, hematemesis, and melena. Once the abdominal phase begins, the disease progresses rapidly and terminates fatally. Laparotomies have been performed in some cases, and usually the findings are yellow plaques scattered over the intestine with minute perforations which cause peritonitis. The cutaneous and intestinal lesions have been found to be due to thromboses of arterioles. A case with cerebral thromboses and neurological findings has been reported in the literature. The disease has been found most commonly in persons between the ages of 15 and 25 years. In one case an elevated gamma globulin and depressed albumin were reported, and in another case the alpha 1 and alpha 2 globulins were elevated. Lesions have also been found in the heart and kidneys. Anticoagulants and

Fig. 3. This shows acute necrosis of the ileum, presumably secondary to vascular occlusion.

Fig 4 This illustrates an acute panarteritis in the serosa of the ileum The accompanying vein is normal

steroids have been used in treatment but seem to be of no help

The condition of the patient under consideration seems to fit rather well the description of Degos disease She had a skin eruption which was followed several months later by intestinal symptoms with progression to death in a few months The description of the skin lesions appears to fit this disease Although peritoneoscopy at the other hospital did not disclose the typical yellow patches on the small intestine they may have been missed or may not have been present at that stage of the disease The renal involvement could also be explained on the basis of Degos disease

DR EISENSTEIN A diagnosis of Degos disease was also made in this patient at Cook County Hospital where a skin biopsy was done The histologic appearance was identical to what has been described in this condition in one phase of the evolution of the skin lesion There was a central ulceration with an abrupt loss of epithelium at its margin The underlying dermis was homogeneous with loss of skin appendages Unfortunately a thrombotic occlusive endarteritis which is thought to be the cause of the skin lesion was not demonstrated in the biopsy here There was however some arteritis at autopsy (Fig 1) Dr Tabin who performed the autopsy found lesions in three locations— the skin the intestine and the kidney The skin lesions (Fig 2) have been described by Dr Phelan In both the small and large intestine there were long but focal areas which grossly and microscopically (Fig 3) consisted of hemorrhagic infarction The mesenteric arteries and veins were carefully dissected and no occlusions were found In small arteries in the wall of the intestine there were foci of acute arteritis (Fig 4) without any cellular proliferation The very acuteness of the reaction suggests that the inflammation was a consequence rather than the cause of the infarctions In areas of

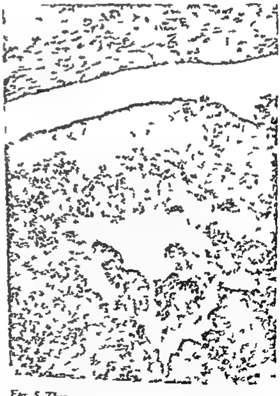

Fig 5 This is a cross section of a recent antemortem thrombus which partly occludes the lumen of a large renal vein

Fig. 6. This shows masses of material resembling fibrin occluding peripheral loops of glomerular capillaries.

necrosis such as this, interpretation of any inflammatory change, whether it be in an artery or anywhere else, must be made with care because, after all, necrosis itself excites an acute inflammatory reaction.

In the kidney there were changes which were not so difficult to interpret but still impossible to explain. Within large veins in the kidney there were multiple bland thrombi (Fig. 5), some of which showed early organization, indicating that they had been there for a few days. Within numerous glomeruli (Fig. 6) the glomerular loops were plugged with eosinophilic masses which were quite similar to those seen in thrombotic thrombocytopenic purpura or afibrinogenemia of pregnancy. There also seemed to be a mild hypertrophy of glomerular cells, particularly epithelial cells.

A few other lesions were seen. One was a rather severe calcification of the elastic fibers of the dermis (Fig. 7). Another was calcification of arteries within the pancreas. The latter finding was accompanied by a rather severe interstitial fibrosis of the pancreas. There was a gallstone. Finally, there were great numbers of large amphophilic cells in the pituitary gland.

Thus, the findings in this patient were in keeping with a diagnosis of Degos disease. *The question now is what is this disease.* As Dr. Phelan has said, Degos and others described this condition in which all manifestations seem to be secondary to a thrombotic and inflammatory vascular disease, anatomically and clinically distinct from either periarteritis nodosa or Burger's disease.

The glomerular and venous thrombi seen here indicate that this disease should best be classified as a venoarteriopathy. The calcifications in the skin and pancreatic artery can perhaps best be explained as sequelae of degenerative changes due to vascular insufficiency and a healed arteritis, respectively. The changes in the pituitary gland must at present be dismissed as being probably unrelated to the disease.

Fig. 7. This is a section of a cutaneous lesion similar to the one seen in Fig. 2. The von Kossa stain reveals calcification of elastica.

So we have a relatively new pathologic and clinical entity and a lethal one. We have nothing concrete on which to base any theories of causation.

DR. TABA: Would you care to speculate about the cause of this condition?

DR. EISENSTEIN: No. For the present all we can do is describe the features of the disease as they appear in patients. The only laboratory approach I can think of is a study of clotting mechanisms, but this has so far been unrewarding.

DR. PHELAN: Do you think that all the changes of this disease are secondary to the vasculitis?

DR. EISENSTEIN: I really am not sure, although the evidence is rather convincing that they are. But we should recall that the skin lesions of periarteritis nodosa and Burger's disease or even Raynaud's phenomenon are different from those of Degos' disease and these are also considered to be secondary to vascular occlusion. But these differences may be related to such things as the size of the vessel occluded, the rate of occlusion, and the local venous circulation. Aside from these considerations a vascular occlusion is a vascular occlusion and should produce the same effects in the tissue supplied by the blood vessel whether it is occluded by a string, an embolus, or anything else. I do want to emphasize that it is important and sometimes difficult to determine whether an arteritis is the cause or the result of an ischemic lesion. The glomerular lesions in this case are of real interest. If glomerular thrombi should appear consistently in these cases it may provide something of a lead, since we are beginning to learn something about the pathologic importance of this kind of lesion. Finally, the intrarenal venous thrombi without demonstrated phlebitis suggest, but do not prove, that a clotting defect may be basic in this disorder.

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Fundamentals of clinical cardiology

The diagnosis of angina pectoris

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There is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it.[1]

The concept that the history is the essential feature in the clinical diagnosis of angina pectoris was established by William Heberden in 1768.[1] In 1964 this is essentially unchanged, but the development of the two step exercise test and advances in electrocardiography have given objective studies. Recent advances in therapy make early and correct diagnosis essential so that appropriate treatment can be instituted. The diagnosis remains dependent upon the history and electrocardiographic changes, and these parameters must be critically evaluated in any patient in whom angina is considered.

History

The classic description of Heberden is partially applicable today. "Those who are afflicted with it are seized while they are walking (more especially if it be up hill and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes."[1]

The difficulty experienced by the patient with angina is appropriately described as a distress or discomfort and not a pain. Frequently they object to the word pain. The distress may be classified according to location, precipitating factors, quality, intensity, and duration. It may vary considerably from person to person but tends to remain constant in the individual patient. It is his discomfort.

1. Location. "The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and more often inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm . . . the pain sometimes reaches to the right arm as well as the left, and even down to the hands."[1]

The location of the distress of angina is related to the sensory innervation of the heart. Fibers originate in the sensory ganglia of the first to fourth thoracic spinal roots and accompany the sympathetic cardiac nerves. With overlapping of sensory nerves and internuncial communications, the cardiac pain dermatomes extend from C_7 to T_6. Roberg[3] states that the extension of the trigeminal nucleus into the cervical chord may explain the location of distress in the lower jaw.

The classic location of anginal distress

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Fig. 1. Ischemic right angle S-T segment depression. Note that the degree of S-T depression is measured from the top of the continuation of the P-R interval.

is in the retrosternal (T_1 to T_4) area, with radiation to the inner aspect of the left arm (T_1), the hypothenar eminence (C_8), and the fourth and fifth fingers (C). The discomfort may radiate to the neck and corresponding areas of the right arm, to both arms, and to the lower jaw. It is important to remember that the distress of angina may occur in only a segment of this distribution, that is, it may be only in the chest, only in the jaw, only in the left arm, or even only in the right arm.

In differentiating anginal distress from psychoneurosis, the psychoneurotic will usually pinpoint his discomfort with one finger, whereas the patient with angina will use his entire hand to designate the area.

2. *Precipitating factors.* The distress occurs with exertion, digestion, excitement, and emotion and is relieved promptly by rest. The discomfort is usually brought on by increased cardiac work. The attacks do not occur regularly each day unless related to exercise or emotion.[4] Angina pectoris may be precipitated by walking up hill after a meal or in the cold or by disturbance of the mind.[1] The distress will frequently respond promptly to nitroglycerin. It has been demonstrated that prophylactic nitroglycerin prevents the anginal distress and eliminates certain abnormal cardiac pulsations which occur during the anginal attacks.[5]

In the psychoneurotic the distressful sensation occurs after the exertion and not during the exertion as is seen in the patient with true angina.

Prinzmetal[4] described a variant form of angina in which the attack is not precipitated by increased cardiac or emotional upsets. It occurs at about the same time each day and is not relieved by rest. The distress is more intense and of longer duration than the classic form of angina and usually disappears dramatically after infarction.

Nocturnal angina pectoris, angina decubitus, is apparently related to the decreased supply of oxygen to the myocardium during recumbency, often associated with pulmonary venous congestion (left heart failure), and occurs primarily when coronary atherosclerosis is complicated by valvular disease, hypertensive heart disease, or cor pulmonale.

3. *Quality and intensity.* Characteristically, anginal distress is described as a burning sensation, tight sensation, or heavy feeling. It may be variously described as strong, constricting, expanding, burning, aching, or pressing. It may be a mild oppression, slight smothering, gassy fullness, sense of weakness or faintness with mild nausea. The arms, hands, and fingers may experience a severe aching, burning, numbness or tingling. There may be an aching, tingling, or bursting sensa-

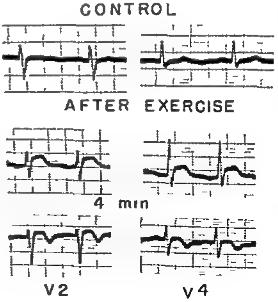

Fig. 2. After exercise the S-T segment elevation in Leads V_2 and V_4 is followed by T wave inversion in 4 minutes and a return to the control in 10 minutes. Several months later the patient had an anteroseptal infarction.

tion in the lower jaw. Very seldom is it sharp so that the patient refers to it as pain.

4. Duration. The anginal sensation usually develops gradually and progressively over a period of 10 seconds to 2 minutes and is constant. It subsides rapidly on rest and particularly after nitroglycerin within a minute or two. Variant forms of angina tend to be more severe and of longer duration.[4] It has been demonstrated by Levine[8] and Freedberg that anginal pain could be relieved by carotid sinus massage. Levine[8] considers this to be diagnostic in many instances. With the patient sitting up and the anginal discomfort present, the right carotid sinus is massaged. If this is not successful, the left carotid sinus is tried, but not both at the same time. Auscultation of the heart is carried out during manipulation, and if significant slowing of the heart occurs, massage is stopped. Massage should not be carried out for more than 3 to 5 seconds at a time. The test is positive for angina pectoris if relief of distress occurs within seconds with usually concomitant slowing of the heart. Since relief occurs at times without slowing of the heart, the carotid massage may be producing an interruption of sympathetic reflex arcs or sensory pathways. A negative response does not rule out angina.

Electrocardiogram

We usually plan on performing a double two-step Master's test, preferably with the patient in the fasting state, rather than beginning with the single-step test. If the patient develops any of his symptoms prior to completion of the required number of trips, the test is stopped and postexercise tracings are taken. In many instances, patients will give a classic description while exercising, yet in relating their histories just before exercise they were very vague. For this reason it is important to be present when the test is performed, as well as to prevent any undue attack of prolonged coronary insufficiency or even occlusion. It is preferable to take Leads V_4 or V_5 (depending on which has the greater R wave amplitude), V_1, L1, and L2 in this order immediately, at 1 minute, 3 minutes, and 5 minutes after exercise. If abnormal change develops, then tracings are taken until there is a return to normal. Radioelectrocardiography during exercise may give additional information, as shown by Bellet and associates.[9] Often attempting to reproduce the patient's symptoms by exposing him to his particular type of precipitating factor may be beneficial, and an electrocardiogram taken at this time may be significant. Abnormal changes have been seen in such instances even though a double Master's test was negative.

Positive electrocardiographic changes after exercise

1. S-T SEGMENT DEPRESSION. For many years the degree of S-T segment depression was considered to be most important. Now the type of S-T segment depression[10,11] is given most attention. When the S-T segment is depressed at a right angle to the vertical, as seen in Fig. 1, a half millimeter or more of depression in con

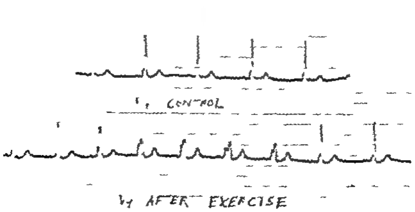

Fig. 3. Intermittent left bundle branch block after exercise.

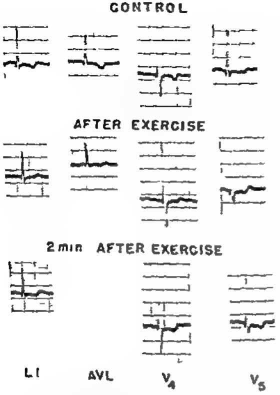

Fig 4 Patient with history of angina and previous old myocardial infarction with residual inverted T waves After exercise the T waves became upright

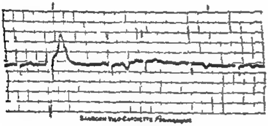

Fig 5 Note inverted T waves which follow the premature ventricular and atrial complexes

sidered to be significant with or without T wave inversion Note that the base line is measured at the upper portion of the continuation of the P R interval as shown by the dotted line The S T change may be present in one or several leads If early repolarization is present in the control the S T segment has to return below the base line to be abnormal Frequently in such cases it becomes isoelectric with exercise

Levy[13] advocated the anoxemia test which is performed by having the patient breathe a combination of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes During this interval electrocardiograms are taken every 5 minutes and significant S T segment depression is noted This test requires special apparatus and is fraught with some danger

2 S T SEGMENT ELEVATION Occasionally after exercise S T segment elevation develops instead of S T segment depression[4] This usually denotes severe ischemia and in our experience indicates that a coronary vessel is on the verge of occlusion Frequently these patients will develop an occlusion in the area in which the S T segment elevation is noted The patient represented by Fig 2 developed S T segment elevation in the V_3 and V_4 positions with exercise After 4 minutes the S T segment became isoelectric with the T waves inverted and after 10 minutes the tracing resembled the control Several months later this patient developed an anteroseptal occlusion and has now been asymptomatic for 4 years

3 BUNDLE BRANCH BLOCK Fig 3 demonstrates the occurrence of intermittent left bundle branch block in the V_4 position after exercise This is significant[9] and usually denotes ischemia of the septal coronary branch

4 INVERTED T WAVES BECOMING UPRIGHT In evaluating a patient with known coronary artery disease especially after infarction it may be necessary to have him perform the exercise test If the inverted T waves become upright this is a significant finding (Fig 4)

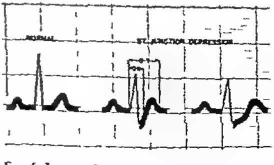

Fig 6 Junctional or J S-T segment depression producing an acute angle Q X and Q T measurements are shown

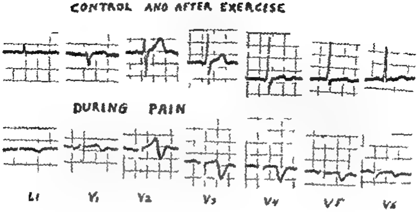

Fig. 7. Negative double Master's test. Tracing taken during pain which occurred each morning reveals inverted T waves greater than 2 mm. with long Q-T interval.

5. T WAVES INCREASING IN AMPLITUDE. If after exercise the T waves, especially in Lead V4, exceed 5 mm. or 300 per cent or more of the resting value,[14,18] ischemia is present. Also the development of an inverted U wave[14] is significant.

Suggestive electrocardiographic changes after exercise.

1. ARRHYTHMIAS. Ventricular or atrial premature beats which occur after exercise and persist over 3 minutes are suggestive of coronary insufficiency, particularly when runs of premature beats or ventricular premature beats from several foci occur. A few premature beats, especially those that occur immediately after exercise and then disappear, are of no significance.

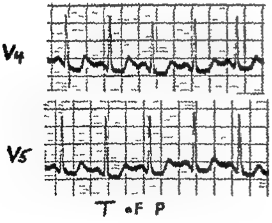

Fig. 8. After exercise the amplitude of the P wave increases and a large T_p wave results in S-T segment displacement which is suggestive of the right angle type. The apparent S-T depression is due to the carry-over of the T_p wave which causes the P-R segment to slope downward.

2. T WAVES INVERTED MORE THAN 2 MM. WITH OR WITHOUT EXERCISE. It is important to consider the many nonsignificant causes of T wave inversion. It is not unusual to see inverted T waves after exposure to cold,[17] smoking,[18] hyperventilation,[19] after a large meal, and in L2, L3 and aVF in so-called suspended hearts,[9] and in patients with early repolarization.[1] Inverted T waves can occur on an autonomic basis after fear, anxiety, or neurocirculatory asthenia. Many other nonspecific etiologies exist. The duration of the Q-T interval should be considered in an evaluation of inverted T waves. If the Q-T interval is prolonged with an inverted T wave and there is no known electrolyte imbalance, this is more suggestive of myocardial ischemia than is T wave inversion with a short Q-T interval,[9] especially if the inversion is more than 2 mm.

3. POSTEXTRASYSTOLIC T WAVE CHANGE WITH OR WITHOUT EXERCISE. This has been referred to as a built-in Master's test.[3] The T wave of the complex which follows a premature ventricular beat and occasionally of that which follows a premature atrial beat is inverted. In the tracing shown in Fig. 5 such changes can be seen in the complexes which follow both the ventricular and atrial premature contractions. Figura[4] did not correlate the phenomena with coronary artery disease.

but we are of the opinion that when this is present it is very suggestive of myocardial ischemia

4 JUNCTIONAL OR J ST SEGMENT DEPRESSION GREATER THAN [illegible] MM This type of ST segment depression does not form a right angle with the vertical but makes an acute angle and there is a constant ascent to the base line The return is rapid or slow but the segment is never entirely horizontal or sagging Only the junction of the QRS with the RS T segment is depressed (Fig 6) Master[10] believes that this type of change is significant and that if the junctional depression is 2 mm or more it is practically always an indication of coronary artery disease In addition he considered to be positive a Q X/Q T fraction of 50 per cent or more or a Q T ratio (actual to normal Q T for rate) of 1 08 or more or both The Q X interval is measured from the beginning of the QRS until it returns to the base line (Fig 6) Levine[3] and Russek[11] have stated that some junctional S T segment depression occurs in

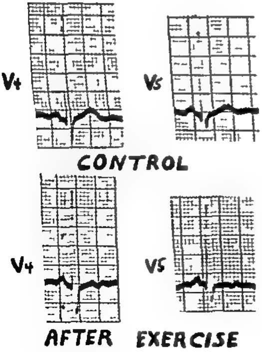

Fig 9 A 20 year-old patient with no evidence of heart disease ... inverted T waves ... than 2 mm with a short Q T interval after exercise

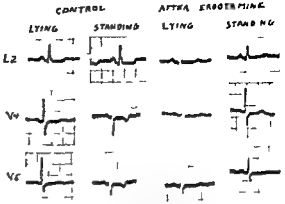

Fig 10 A 35 year-old woman with no evidence of heart disease in whom the labile T waves inverted when she was standing but not after she had been given a sympatholytic drug ergotamine (0 5 mg intramuscularly)

normal individuals after exercise We believe at present that if the junctional S T depression is 2 mm or greater and especially if it persists for longer than 2 minutes and the ascent reaches the base line at 0 08 second or greater it is suggestive of myocardial ischemia

Positive or suggestive electrocardiographic changes during distress This phenomenon of positive or suggestive electrocardiographic changes which occur spontaneously during distress is of the same significance as positive or suggestive changes which occur with exercise The patient represented by Fig 7 had a normal control and double two step Master s test He experienced an ache in his jaw on the right side in the early mornings just after drinking coffee He did not have any chest sensation Note the T wave changes recorded during one of these morning periods

Negative or false positive electrocardiographic changes after exercise

1 JUNCTIONAL OR J ST SEGMENT DEPRESSION LESS THAN 2 MM As stated previously it has become apparent that the type of S T segment depression is of more significance than the degree of depression We consider junctional S T depression to be suggestive only if it satisfies the criteria above otherwise it is negative

2 T OF P DEPRESSION The most clearly recognizable evidence of atrial repolarization is the T_p wave which follows the P wave and is normally of opposite pol

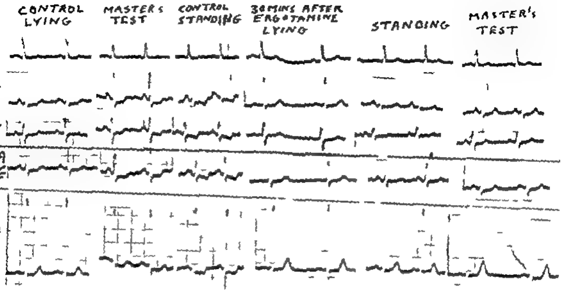

Fig. 11. False positive Master's test with right angle S-T segment depression also produced by standing. After 0.5 mg. of ergotamine there are no changes on standing or after a double Master's test.

This deflection usually results in a P-R segment located at a different level than the isoelectric T-P segment, and it usually extends into and beyond the QRS complex and influences the level of the S-T segment. There is evidence of a direct relationship between the area of the normal P wave and that of the T_p wave which follows. Thus in the presence of a large P wave a large T_p wave may be expected and S-T segment displacement as a result of this latter wave is likely. After exercise the amplitude of the P wave increases[5] and large T_p waves result in S-T segment displacement as seen in Fig. 8. This S-T segment superficially resembles the right angle type; however, on close inspection it is noted that the apparent S-T depression is due to the carry over of the T_p wave which causes the P-R interval to slope downward instead of straight.

3. T WAVES INVERTED LESS THAN 2 MM. WITH OR WITHOUT EXERCISE. It has been stated previously that T-wave inversion may be produced by a variety of activities. This should be re-emphasized. The patient represented by Fig. 9 has no heart disease but after exercise there is a slight inversion of the T wave, less than 2 mm. There is no significant S-T segment depression and the Q-T interval is short. The patient has been completely asymptomatic and without evidence of heart disease for 7 years since this tracing was recorded. However, dismissal of early electrocardiographic changes as insignificant must be given careful scrutiny, especially in the light of other findings.[18] The pendulum must not be allowed to swing so far that all minor or fluctuating T-wave changes are considered to be nonsignificant.

4. AUTONOMIC CHANGES WITH OR WITHOUT EXERCISE. Increased sympathetic stimulation may produce inverted T waves and S-T segment changes which appear to be significant and give a false positive test.[24, 25] These sympathetic changes can be shown in electrocardiograms taken with the patient in different positions, and can be blocked by sympatholytic drugs such as ergotamine (Fig. 10). The patient represented by Fig. 11 was a 39-year-old white woman who was considered to have angina because of a positive Master's test. Her symptoms were those of the hyperventilation syndrome. The control tracing recorded when she was in the supine position was within normal limits, but when she stood, right angle S-T segment depression and T-wave inversion developed in Leads II, III, aV_F, and V_4. The same changes also occurred after a double two-

step Master's test. Thirty minutes after she had been given 0.5 mg. of ergotamine intramuscularly, the tracing was normal while she was in the supine and standing positions and after a double two-step Master's test. However, all ST-T changes in tense individuals should not be minimized, for an occasional case of asymptomatic coronary sclerosis with associated myocardial damage may be missed. In a double-blind evaluation, Friedberg[9] found a high percentage of false positive results in nonanginal cases.

5. MISCELLANEOUS FALSE POSITIVES. After exercise, secondary ST-T changes (opposite in direction and proportionate in magnitude to the main deflection of the QRS complex in area) may occur in the presence of hypertrophy or bundle branch block patterns and in the Wolff-Parkinson-White syndrome. In our series, 7 exercised patients with the Wolff-Parkinson-White syndrome had right angle S-T depression. False positives can also occur in digitalized patients or in those with healed pericarditis, at times even when the resting tracings are normal. The effect of digitalis on the S-T segment and the T wave may be altered by many hemodynamic factors; therefore, one cannot in

Table I. Results of Master's two-step test

		Completed test	Incompleted test
Patients with angina			
Total number	190	98	92
Positive	110 (57.9%)	54 (55.1%)	56 (60.8%)
Suggestive	27 (14.2%)	21 (21.4%)	6 (6.6%)
Negative	53 (27.9%)	23 (23.5%)	30 (32.6%)
Normal subjects			
Total number	160	150	10
Positive	7 (4.4%)	7 (4.6%)	0
Suggestive	2 (1.2%)	2 (1.4%)	0
Negative	151 (94.4%)	141 (94.0%)	10 (100%)

Table II. Incidence of electrocardiographic response to exercise

Electrocardiographic change	*Of 190 patients with angina (Number and per cent of patients)*	*Of 160 patients with no angina (Number and per cent of patients)*
Positive	110 (57.9%)	7 (4.4%)
Right angle S-T depression of .5 mm. or greater	104 (54.7%)	7 (4.4%)
S-T elevation	2 (1.1%)	0
Bundle branch block	2 (1.1%)	0
T waves increased 300 per cent in amplitude or 5 mm.	2 (1.1%)	0
Suggestive	27 (14.2%)	2 (1.2%)
Arrhythmias	7 (3.6%)	1 (0.6%)
Inverted T waves > 2 mm.	10 (5.3%)	0
Junctional S-T depression > 2 mm.	10 (5.3%)	1 (0.6%)
Negative	53 (27.9%)	151 (94.4%)
Junctional S-T depression < 2 mm.	4 (2.1%)	9 (5.6%)
T of P depression	1 (0.5%)	4 (2.5%)
Inverted T waves < 2 mm.	0	4 (2.5%)
No change	[illegible]	[illegible]

terpret an exercise test in a patient who is receiving digitalis. In fact, in the digitalized patient, tilting to the upright position or the taking of a deep breath can produce distinct S-T changes.

Using the above outlined criteria, we have analyzed the double Master's exercise test in 350 patients with normal resting electrocardiograms from the private practice of one of us (P. C. G.). One hundred ninety of these patients had a definite history of angina, and 160 had a negative history. Table I summarizes the findings in those who completed and those who did not complete the test. Eighty-two of the patients with known angina could not complete the test because angina developed during exercise, and 10 could not complete the test because of dyspnea, dizziness, or tiredness. Table II lists the incidence of the various electrocardiographic responses in both categories. Right angle S-T depression comprised 95 per cent of the 110 positives, 54.7 per cent of the 190 patients with angina.

A separate group of 7 patients with angina who had inverted T waves in the control tracing was exercised, and the T waves became upright. Of 7 patients with ... infarction and angina, right angle S-T depression developed in 2 and the T waves became upright in 2. Seven patients with a negative history and the Wolff-Parkinson-White syndrome developed right angle S-T depression after exercise.

Summary

The diagnosis of angina pectoris is dependent upon the history and electrocardiographic changes. It should be emphasized that electrocardiographic changes must be interpreted with a knowledge of the clinical history, so that the significance of suggestive changes is more apparent.

The difficulty experienced by the patient with angina is characterized as a distress or discomfort and not a pain. The discomfort is provoked by exertion, digestion, excitement, and emotion, and is classically located in the retrosternal area with radiation to the inner aspect of the left arm, the hypothenar eminence, and the fourth and fifth fingers. The distress may radiate to the neck, the right arm, and the jaw, and may occur in only a segment of the distribution. It develops gradually over a period of 10 seconds to 2 minutes and is relieved promptly by rest or nitroglycerin. It may also be relieved by carotid sinus massage.

It is usually wise to perform a double two-step Master's test, with the test discontinued if the patient develops discomfort. Positive electrocardiographic changes after exercise include (1) right angle S-T segment depression of 0.5 mm. or more, (2) S-T segment elevation, (3) bundle branch block, (4) inverted T waves becoming upright, and (5) T waves increasing 5 mm. or 300 per cent in amplitude, or inverted U waves. These changes are also significant if they occur spontaneously during the period of anginal distress. Suggestive electrocardiographic changes after exercise are (1) arrhythmias, (2) inverted T waves with or without exercise, especially if the inversion is more than 2 mm., (3) postextrasystolic T wave change with or without exercise, and (4) junctional S-T segment depression greater than 2 mm. Negative and false positive changes after exercise include (1) junctional S-T segment depression of less than 2 mm., (2) T of P depression, (3) inverted T waves less than 2 mm., with or without exercise, (4) autonomic changes, and (5) false positive results in patients with hypertrophy, bundle branch block, Wolff-Parkinson-White syndrome, after digitalization, or pericarditis.

A double Master's exercise test was analyzed in 350 patients with normal resting electrocardiograms. One hundred and ninety had a definite history of angina, with positive changes in 57.9 per cent, suggestive changes in 14.2 per cent, and negative changes in 27.9 per cent. One hundred and sixty had a negative history, with positive changes in only 4.4 per cent, suggestive in 1.2 per cent, and negative in 94.4 per cent. Of 14 patients with coronary disease and inverted T waves in the control tracing, 2 had right angle S-T depression, in 9 the T waves became upright, and in 3 there was no change.

With improving methods of therapy, correct and early diagnosis is essential in the proper management of the patient with angina pectoris.

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Diuretic therapy. Part I

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The use of diuretics to control the retention of salt and water in cases of congestive heart failure is an essential part of treatment after digitalis and the dietary restriction of salt have become inadequate. Considerable advances in diuretic therapy in the past decade have greatly increased the ease and efficacy of treatment, but have also introduced new complications.

With the great increase in the number of [illegible] agents, a multiplication of trade names has evolved, not only of the single drugs but also of combinations of drugs. This all leads to confusion. Because of this, it is thought to be desirable to review and re-evaluate these agents, their modes of action in so far as they are known, their differences, and especially their clinical value.

We will consider first the diuretics of minor natriuretic capability, which now have only a limited or specialized role in cardiac therapy.[1] Mercurial diuretics, thiazides,[2] aldosterone antagonists,[3] and recently developed new potent diuretics will be discussed in future articles.

Osmotic diuretics. Nonionic osmotic diuretics, such as urea or mannitol, are now rarely used in the treatment of congestive heart failure. When given intravenously, they produce intracellular dehydration by drawing water from the cells to re-establish osmotic equilibrium.[4] Mannitol can only be given intravenously. Urea is available for both oral and intravenous use and is an effective osmotic diuretic in either case. Both substances are filtered by the glomerulus. Mannitol is not metabolized, nor is it reabsorbed or secreted by the renal tubules. At low rates of urine flow, some endogenous urea is reabsorbed, but when urea in large quantities is used as a diuretic, it may be considered to be essentially unreabsorbed. Thus, both agents add a large quantity of osmotically active material to the glomerular filtrate and prevent the tubular reabsorption of water while the water is held in the filtrate to maintain osmotic balance. Because of this retention of water in the filtrate, concentration gradients of electrolytes develop while they are absorbed partially without water. This limits their reabsorption and causes a urinary loss of some electrolyte.

Although this prominent water diuresis and modest natriuresis are not generally used now in the treatment of congestive heart failure, either urea or mannitol is occasionally used to provoke a water diuresis in a patient with dilutional hyponatremia. Either drug is used more frequently diagnostically in split renal function tests or in the late washout modification of the intravenous pyelogram. In either case, the water diuresis produced

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serves to exaggerate the difference in the water reabsorbing characteristics of the two kidneys in renovascular hypertension. The major clinical use of urea is in neurosurgery, where its effect, intracellular dehydration, is used to reduce cerebral edema. Mannitol has recently been recommended as an osmotic diuretic to increase barbiturate clearance in barbiturate intoxication and to prevent renal failure after a hemolytic transfusion reaction by reducing the formation of hemoglobin casts. It has also been shown that the prompt institution of a mannitol osmotic diuresis can protect against acute renal failure in patients who are already oliguric from other causes, such as surgical shock or burns. How the osmotic diuresis affords protection in this situation is not known. Furthermore, when used with bicarbonate to maintain an alkaline pH, osmotic diuresis with mannitol may afford some protection against the renal shutdown which is associated with acute uric acid load after chemotherapy of lymphoma. (See Table I.)

Acidifying salts. Ammonium chloride, the acidifying salt used most commonly, is given by mouth. It is not an osmotic diuretic. Although its only important use is the potentiation of the effect of mercurial diuretics, apparently by an increase in the serum chloride, it does have some independent diuretic activity. In the past this has been thought to be due to a reduction in the ability of protein to bind water or to an effect of acidosis on renal tubular enzymes. Ammonium chloride, which is converted in the liver to urea and chloride, increases the level of serum chloride and the amount of filtered chloride. The reabsorption of some of this excess chloride into renal tubular cells probably blocks the secretion of hydrogen ion in the hydrogen-sodium exchange mechanism of the distal tubule, thus producing an increased excretion of sodium. This results in a mild diuresis, which is limited in 2 or 3 days by the development of acidosis and a compensatory increase in the tubular production and excretion of ammonia. Ammonium chloride frequently causes gastric irritation and even nausea and vomiting; this further limits its usefulness.

The use of enteric-coated tablets decreases these gastrointestinal side effects but introduces the problem of variable absorption.

L-lysine *monohydrochloride*, originally marketed as a geriatric amino acid supplement, is another salt which produces chloruresis and systemic acidosis. When given as a liquid in milk or juice, it is fairly palatable and produces less gastrointestinal irritation than does ammonium chloride. It has no independent diuretic activity but can potentiate the effect of mercurials.

Ammonium chloride can occasionally produce hepatic coma when used in patients with severe liver disease. L-lysine

Table I. Osmotic diuretics

Preparations	*Dosage forms*	*Dose*
Urea (N.F.)	Crystalline powder	Oral—8 to 40 Gm. one to four times a day in fruit juice
Mannitol (N.F.)	25 per cent, 50 ml. vial	50 to 100 Gm. as 25 per cent solution

Table II. Acidifying salts

Preparation	*Dosage forms*	*Dose*
Ammonium chloride (N.F.)	300 mg. tablets 300 and 500 mg. enteric-coated tablets	Between 4 and 12 mg. a day, usually 8 Gm.
L-lysine monohydrochloride	Solution of [illegible] Gm. per 30 c.c.	10 Gm. three tim

An improved technique of external cardiac compression in infants and young children

External cardiac compression is now the accepted method of treating sudden cardiac arrest. The technique finds its widest application in the first years of life since this emergency arises nearly three times as frequently in infants as in all other age groups.[1] In our hospital about 7 out of [illegible] autopsied patients have been treated with closed chest compression. Small size and pliability of structures lend themselves to effectiveness but trauma may also be easily produced.

The most common serious complication is rupture or tear of the liver.[2] Mechanisms of production and prevention of such trauma were investigated and the technique modified. Circulatory studies to test the effectiveness of the evolved method were also performed.

Fifteen infants and young children selected according to criteria which ruled out previous damage were subjected to pressures up to 60 pounds per square inch. Pressures were concentrated at various points on the anterior thoracic surface in one group of subjects, the abdomen was selectively compressed in another, and both chest and abdomen were simultaneously compressed in a third group. Apart from superficial tears of the liver capsule caused by sudden sharp pressures of the finger tips over the xiphoid, the only serious trauma occurred when thorax and abdomen were compressed simultaneously. In all such cases the liver was ruptured when its downward excursion was thus prevented by elimination of abdominal space.

These results showed that moving the site of thoracic compression away from the xiphoid end of the sternum prevented injury to the liver. To determine the position of the infant heart relative to the sternum, chest radiographs of 20 infants and young children were taken using lead markers to pinpoint the position of the sternal notch, mid-sternum, and xiphisternal junction. The relative downward progression of the heart at various ages from prematurity to 5½ years was thus demonstrated. In infants the ventricles lie behind the mid-sternum, whereas the lower sternum extends over the liver.[3] Pressure over the mid-sternum is directly transmitted to the ventricles, whereas compression of the xiphisternum affects the liver.

Twenty cadavers were used to evaluate circulatory pressures produced by mid-sternal and lower sternal pressures. An open circulation was assured by intracardiac injection of heparin; external pressures were measured by a bag and gauge arrangement, and resulting systolic pressures were recorded on a mercury manometer connected to an intra-aortic catheter. The results showed that in infants circulatory pressures obtained by mid-sternal compression were equal to, or slightly higher than, those obtained by pressing over the lower sternum; in young children similar blood pressures were obtained in both locations. A cineangiographic record taken during mid-sternal compression demonstrated the circulation of blood through the body.

The modified technique of external cardiac compression in infants and young children consists in compressing the *mid sternum* with superimposed *thumbs*. This point is readily found halfway between the sternal notch and the xiphisternal junction. The operator's fingers are linked behind the infant's back for additional support, and the head is held toward the operator. Mouth-to-mouth ventilation can be applied without difficulty or confusion by a single operator; approximately one inflation after each five compressions is administered while the thumbs are lifted off the chest. An electrocardiogram should be obtained as soon as possible, and external defibrillation carried out in cases of ventricular fibrillation.

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Effect of sex difference in digoxin toxicity

In addition to their more obvious properties estrogens have recently been in the spotlight because of their possible role in the modification of atherosclerosis. In a different vein recent experimental work has suggested that estrogens may have a protective effect in digitalis toxicity.[1,2]

Since much of the laboratory work performed in the past on digitalis has not considered the sex of the animals studied we thought that further exploration of the possible sex differences in digitalis tolerance would be of interest.

Since the previous work on this subject utilized dogs of varying pedigrees ages and sizes two groups of rabbits of identical age breed size and nutrition were studied; the only obvious difference between the two rabbit populations was sex. A standard digitalis bioassay[3] was performed using digoxin 0.8 mg per kilo per hour infused intravenously. The end point of the bioassay was cessation of all electrical activity for 60 seconds on a continuous electrocardiogram.

The bioassay of digoxin in the 21 male rabbits was 94.7 minutes with a range of 51 to 130 minutes. However the identical bioassay in the 19 female rabbits was 123.4 minutes with a range of 86 to 194 minutes. An autopsy was performed on all the rabbits to insure that the females were not pregnant.

The difference between the two groups is significant to a p value of less than .001 (Student's t test).

If sex does alter tolerance to digitalis in animals the scope of possible ramifications might be considerable. It is interesting to contemplate that the sex factor heretofore largely ignored may be of importance in both clinical and experimental studies with the digitalis glycosides.

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Phenacetin nephritis

Recent experience suggests that we in this country have been slow to recognize a form of chronic renal disease that has been attracting considerable attention in Europe for the past 10 years. This is the association between chronic renal failure and the heavy use of analgesics which contain phenacetin. Since the first publication by Spuhler and Zollinger in 1953 there have been an increasing number of reports of this association from Germany, Switzerland and Scandinavia and more recently from England, Canada, South Africa, Australia and New Zealand. The renal lesion has been described as an interstitial fibrosis and inflammation with a strikingly high incidence of papillary necrosis.

Very few cases of this type have been reported in the American literature. Since becoming aware of the European data in 1959 I have encountered 13 patients who had taken huge quantities of analgesics and who had serious chronic renal disease. These were drawn from one university a large county hospital in addition to a few referred private patients. It is difficult to believe that I saw no similar cases prior to 1959 or that there are not many more of them throughout the country.

The majority of these patients were neurotic women. In all but one case chronic headache was the stated reason for the daily ingestion of analgesics in large amounts (8 to 20 tablets per day of Anacin, APC, Empirin compound or Percodan) often concealed or minimized and extended over many years. The major clinical features of the renal disease were hyperazotemia, anemia, and sometimes polyuria, with hypertension and proteinuria being relatively mild. Abnormalities in the urinary sediment were few except for the frequent presence of bacteriuria and pyuria. Nine of the 13 patients had positive urine cultures. Two had secondary renal tubular acidosis of the type seen in chronic nephritis.

Two patients have been lost

have died and 6 continue to have hyperazotemia in spite of alleged cessation of ingestion of phenacetin. Improvement has been minimal in 2 patients who have been followed for over 2 years after phenacetin was stopped.

Dr. Hugh Edmondson, Professor of Pathology, believes that the pathologic changes are recognizable and distinct from those caused by pyelonephritis alone. There is a high incidence of severe papillary necrosis without extensive polymorphonuclear exudate. One sees remarkable atrophy of tubules and peritubular capillaries in the medulla, focal areas of tubular atrophy in the cortex, and an increase in round cells and fibrous tissue in the interstitium. Many of the tubular cells show a positive iron stain. Such glomerular changes as are present appear to be secondary.

Since animal experiments have not conclusively demonstrated this type of phenacetin toxicity, many pharmaceutical manufacturers think that it is unfair and unscientific to blame phenacetin in preference to aspirin or caffeine. Nevertheless, it is my own conviction that if we look carefully for patients with hyperazotemia and chronic headaches, we will find increasing numbers who have abused analgesics and that phenacetin will eventually be shown to be the reason for their renal disease. It is to be emphasized that there is no evidence of damage from ordinary use of phenacetin, so that there seems to be no reason for placing controls on its distribution.

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The circulatory effects of synthetic vasopressin in cirrhosis of the liver

Gastrointestinal bleeding as a result of portal hypertension constitutes a serious hazard, and because of the underlying liver disease emergency surgery is often not feasible. For this reason attempts have been made to find agents which will lower portal venous pressure, and of these the most popular in current use is vasopressin (Pitressin). Kehne, Hughes and Gompertz[1] were the first to use vasopressin for the control of bleeding from esophageal varices, and since then a number of workers have reported their experiences with this agent. Its effect in reducing portal venous pressure has been known for many years as a result of experiments in animals,[2,3] but its precise mode of action has only recently been investigated in man.

The influence of natural vasopressin (given as a single injection or short intravenous infusion) on various regions of the circulation has been studied separately in man, and it has been shown to cause a fall in portal venous pressure[4,5] and splanchnic blood flow,[6] no essential change in cardiac output,[7] and variable changes in the pulmonary circulation.[8,9] It has been suggested that vasopressin lowers portal pressure by increasing the vascular resistance of the splanchnic bed, and, on the assumption that cardiac output was unchanged,[7] it had been implied that vasopressin had a greater constrictive effect upon the splanchnic circulation than elsewhere. Such a conclusion cannot be deduced reliably in the absence of simultaneous measurements of cardiac output.

In a recent investigation,[10] the effects of synthetic vasopressin (Octopressin; Sandoz), the phenylalanine derivative of lysine vasopressin (PLV 2),[11] upon the systemic, pulmonary and splanchnic circulations were studied simultaneously in patients with cirrhosis of the liver and portal hypertension. The circulatory effects of another synthetic pressor agent, angiotensin II, were also studied and compared to the hemodynamic changes due to vasopressin.

After measurements were made in the control period, synthetic vasopressin was infused into the superior vena cava by a constant infusion pump in a dosage that ranged between 0.10 and 0.16 units per minute in a volume of 2.0 ml. over 32 minutes (approximately equivalent to a total of 20 units of natural vasopressin). Effects were observed during the infusion period and for 56 minutes afterward. Changes in splanchnic blood flow were inferred from changes in hepatic arteriovenous oxygen difference, assuming that there was no change in splanchnic oxygen uptake during the period of observation. Although there is no evidence either for or against this assumption, the authors considered it to be a reasonable approximation in view of the unchanged total oxygen uptake of the body. In patients with advanced cirrhosis (as judged by the level of wedged hepatic venous pressure) they have found that measurement of splanchnic blood flow by the Bromsulphalein clearance method is unreliable.

During the period of infusion there was a prompt and sustained rise in the brachial arterial pressure. The pulmonary wedge and pulmonary arterial pressures increased throughout the infusion, reaching the highest value at the end of the infusion. The rises in pulmonary arterial and wedge pressures

were similar so that the difference in pressure across the lung ΔP remained unchanged. At the same time there was a fall in heart rate and a reduction in cardiac output in every patient; the cardiac output continued to fall throughout the infusion. The decrease in cardiac output was on the average greater than the fall in heart rate so that there was also a significant fall in stroke volume. During the recovery period the elevation of brachial arterial pressure persisted for some 30 minutes and then gradually returned to the level before the infusion. Similarly there was a gradual fall in the pulmonary intravascular pressures but the heart rate and cardiac output were still lower than before the infusion even 56 minutes after the infusion was stopped. With the rise in brachial arterial pressure and fall in cardiac output during the infusion there was a gradual rise in right atrial and free hepatic venous pressure and a reduction in wedged hepatic venous pressure which was greatest at the beginning of the infusion. Hepatic venous oxygen saturation fell and the hepatic arteriovenous oxygen difference increased. On the assumption that splanchnic oxygen uptake remained unaltered this indicated that splanchnic blood flow fell to 59 per cent of the preinfusion value, whereas the cardiac output fell to 63 per cent of the initial value. After the infusion was stopped these values slowly returned but did not reach their initial levels by the end of the study.

The influence of atropine on the effects of vasopressin was studied in one patient. Vasopressin still caused a substantial fall in cardiac output and stroke volume after atropine in the absence of any change in heart rate.

The effects of angiotensin on the systemic and pulmonary circulations of patients with cirrhosis of the liver were similar in all respects to those previously observed in normal subjects.[3] In the splanchnic circulation angiotensin also caused a fall in hepatic venous oxygen saturation and it was deduced that the percentage fall in splanchnic blood flow was of the same magnitude as the fall in cardiac output although these changes were not so great as those observed with vasopressin. At the same time angiotensin caused a marked rise in free hepatic venous pressure but in contrast to vasopressin there was a rise in portal venous pressure in each patient studied.

From this investigation the authors concluded that synthetic vasopressin had a marked pressor action on the systemic arterial circulation and little direct effect upon the pulmonary circulation. The fall in cardiac output was due to a direct depressant action of vasopressin upon the myocardium acting either directly or indirectly through coronary vasoconstriction which has been shown to occur in experimental animals. The gradual rise in pulmonary wedge pressure which reached a maximum at a time when both cardiac output and stroke volume were most reduced suggested a relative failure of the left ventricle and by similar argument the rise in right atrial and free hepatic venous pressure might be attributed to a rise in right ventricular end-diastolic pressure.

The observed change in hepatic arteriovenous oxygen difference indicated a fall in splanchnic blood flow comparable to the fall in total cardiac output. This was taken as strong evidence that vasopressin did not, as was previously implied, have a greater constrictive effect upon the splanchnic blood vessels than elsewhere. The findings suggested that the fall in cardiac output together with the generalized arteriolar vasoconstriction resulted in a fall in splanchnic blood flow and a concomitant fall in portal venous pressure. The authors raised the question of the validity of their assumption that splanchnic oxygen uptake remained unaffected by vasopressin and argued that since total oxygen uptake fell slightly but insignificantly during the period of infusion and since side effects on the bowel were absent it was unlikely that splanchnic oxygen uptake increased significantly. If, however, the splanchnic oxygen uptake did increase because of increased motility of the bowel, the splanchnic blood flow would have decreased less than was deduced and proportionately less than the cardiac output. This would suggest that splanchnic vascular resistance must have increased proportionately less than did the resistance of the rest of the systemic circulation.

Some of these observations differed in some respects from those reported in studies using natural vasopressin and have been attributed in part to differences in chemical structures.

In contrast to vasopressin, angiotensin caused a rise in portal venous pressure at a time when splanchnic blood flow fell. This rise together with the simultaneous marked elevation in the pulmonary wedge, right atrial and free hepatic venous pressures suggests that angiotensin may cause generalized venous as well as arteriolar vasoconstriction.

Conservative measures for control of hemorrhage from esophageal varices are still far from ideal and clinical experience indicates that vasopressin does not consistently stop bleeding. Nevertheless, in the absence of other more suitable agents occasional success may be achieved with vasopressin. The authors stress that since synthetic vasopressin causes a prolonged depression of cardiac output it should be used with caution for controlling hemorrhage especially if there is evidence of associated ischemic heart disease.

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Letter to the Editor

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February 8 1964

To the Editor

I am grateful to Professor Wright and Dr Fahs-Beck[1] for the attention they have devoted to some of the points raised in my annotation[2] but my doubts have not been resolved. If comparability of two groups of patients depends upon random selection and a study is planned accordingly then failure to secure random selection must raise doubts as to comparability. These doubts are not dispelled by the results of subsequent analysis of the data collected in the study.

It does not appear to me that I grossly misrepresented the authors of the Report[3] when I wrote that they assumed all secondary myocardial infarction to be *potentially* preventable by anticoagulant therapy. If a treatment is believed to have preventive value then to obtain the maximum benefit from its use one must assume *potential* effectiveness in every case and treat as many cases as possible. In a recently published study of myocardial infarction 92 per cent of the patients received anticoagulants. Routine treatment is generally understood to mean treatment of every case in which there is no known contraindication. In the Report the following statement appeared (p 347)

The only medical grounds for excluding such patient from anticoagulant protection would appear to be the chance that they may be harmed thereby either (1) because contraindications point in specific cases to an excessive risk of hemorrhage or (2) because adequate medical or laboratory safeguards for the proper administration of anticoagulants are unavailable.

It appears that I was wrong in interpreting this statement as advocacy of routine treatment and I hasten to acknowledge that Professor Wright now recognizes many contraindications including numerous conditions involving patient and in addition many other factors. If this means that the number of patients who can receive anticoagulants is substantially less than 100 per cent then claims for the value of this treatment in myocardial infarction must be correspondingly moderated. Perhaps Professor Wright would indicate what proportion of his patients actually do receive anticoagulant and it will then be possible to estimate the reduction factor which must be applied.

I drew attention to the uneven mixture of ward patients and private patients in the study and to the possible effect of this on comparability of the treatment and control groups. Professor Wright has sought to allow for this factor by adjusting his figures in such a way that the pr[…] of ward and private cases is the same in the control and treated groups as in the total sample. I preferred to eliminate the factor altogether by confining the comparison between controls and treated cases to the 8 hospitals which contributed only ward cases. This produced a group of 308 patients relatively uniform in respect of hospital care and showing no significant difference in mortality between controls and treated cases. Is it Professor Wright's contention that this group is not large enough to reveal the substantial advantage which he claims is conferred by anticoagulant therapy? If this be so then some of the other conclusions of the Report must come under question. For example it is hardly permissible to draw any statistical conclusions from 91 autopsies representing less than 50 per cent of fatal cases and selected by factors quite incapable of analysis. Many of the other statistical studies which Professor Wright cites in his support would also have to be discounted.

The over all difference in mortality between ward patients and private patients is of interest for other reasons. It demonstrates the inadequacy of a *post facto* examination of the character of two groups as a means of showing that they are comparable. The application of such tests to ward patients and private patients failed to show any difference between them (p 324) yet the difference in mortality indicates that there must have been an important difference. There is a brief mention of the possibility of a difference in general physical condition but the authors of the Report assumed that differences in nursing care could have been the main factor. I am unwilling to accept this explanation for I cannot believe that in American hospitals of world reputation the nursing care of ward patients is so inadequate as to account for a net loss of 7 lives per hundred hospitalized cases of myocardial infarction.

I must agree that the three pairs of comparative mortality studies which I mentioned did not represent a balanced survey of all such studies (this unrewarding task could hardly have been undertaken in an annotation approximately half the length of Professor Wright's reply). As I stated they were quoted as examples and my attention was devoted mainly to the American Heart Association study which has been largely responsible for the subsequent widespread use of anticoagulants in myocardial infarction. An eminent American medical statistician has recently expressed the attitude which ought to be adopted by the investigators in studies of this kind: "... if we took our data to a statistician off[e]r an investigation we would choose one whose office would merit the title ... water department. We would vie with ... tician in the hunt for defects in our

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